U.S. EPA HIGH PRODUCTION VOLUME
CHEMICAL VOLUNTARY TESTING PROGRAM

CATEGORY ANALYSIS DOCUMENT
AND
UPDATED CATEGORY JUSTIFICATION
AND
TEST PLAN

XYLENOL ISOMERS

Submitted by:
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May 2006

INTRODUCTION

On May 12, 2003, Merisol USA LLC (Merisol) submitted a Category Justification and Test Plan for Mixed Xylenol Isomers. The Category consisted of all six structural isomers of xylenol and is described in detail below. Testing that was conducted following the 2003 submission consists of the following:

Acute algae toxicity
Acute Daphnia toxicity
Bacterial mutation
In vitro mammalian cell chromosome aberration
Mammalian acute oral toxicity
Mammalian repeated-dose toxicity and reproductive/developmental toxicity.

The results of these tests are summarized in Appendix A -- ROBUST SUMMARY FOR MIXED XYLENOL STUDIES SUPPORTING THE XYLENOLS CATEGORY. As with the methyl phenol (cresols) series of isomers, the isomers of xylenol exhibit related toxicity based on the similarity of their structure. Thus, the additional testing conducted further supports the Mixed Xylenols Category.

Mixed Xylenols

Xylenols are liquids or crystals recovered from petroleum streams, coal coking operations and coal gasification. Several isomers are also produced synthetically. Xylenols are isomeric forms of dimethyl phenol containing two methyl groups attached to the ortho, meta, or para positions of the phenol ring. There are six possible isomeric forms of xylenol: 2,3-xylenol; 2,4-xylenol; 2,5-xylenol; 2,6-xylenol; 3,4-xylenol; and 3,5-xylenol. The boiling point range for these isomers is 201.1°C to 227°C.

Merisol's Process

Merisol's phenolic products are highly versatile materials that are used as intermediates in the manufacture of a wide variety of industrial products such as resins, flame retardants, antioxidants, and insulating varnishes. Merisol production of phenolics is essentially a recovery, purification, and fractionation operation. Merisol feedstocks are generally secondary streams from refineries, coal coking operations and coal gasification. From these feedstocks a multi-component phenolic mixture called "crude cresylic acid" is produced, which is composed of phenol, cresols, xylenols, ethylphenols, and, to a lesser extent, other higher boiling alkyl phenols. This mixture is processed to remove impurities, and then separated into various fractions by distillation. Distillation produces phenol, o-cresol, m- and p-cresol mixture, and fractions containing varying compositions of xylenols, ethylphenols, and higher boiling alkyl phenols. Merisol also has a proprietary process that produces p-cresol and m-cresol from the m-cresol and p-cresol mixture produced by distillation. Because of similarities in boiling points of

components in the starting phenolic mixture, isolation of all pure xylenol isomers by distillation is not possible.[1]

Exposure Pattern for Mixed Xylenols

Merisol sells pure phenol, o-cresol, m-cresol and p-cresol. These are also sold in blends, as are the mixtures of xylenols and ethylphenols. The vast majority of xylenols and ethylphenols that Merisol produces and sells are contained in mixtures.[2] Therefore, public (and employee) exposure, as well as potential environmental exposures to Merisol's products, are primarily to blends and mixtures containing xylenols and/or ethylphenols. Because these Merisol products are generally moved into commerce as starting materials for further chemical processing, there is little consumer exposure to xylenols and ethylphenols. Merisol is by far the major, if not sole, U.S. producer of xylenols except for 2,6-xylenol (which is already the subject of a SIDS dossier).[3]

Merisol is a custom blender of phenolics. The number of different phenolic mixtures Merisol typically produces in a year is approximately 50, but can go as high as 100. These mixtures contain varying compositions of phenol, cresols, xylenols, ethylphenols, and higher boiling alkyl phenols. Xylenols, as well as ethylphenols, phenol, and cresols, are not components of every Merisol product mixture.

A breakdown of numbers of xylenol isomers contained in product mixtures is given in Text Table 1. Table 1 illustrates that Merisol products containing xylenol isomers (other than 2,6-xylenol which is already the subject of a SIDS dossier) include two to six different isomers in the products and that more than 60% of the xylenol products sold by Merisol have five or six xylenol isomers. The Merisol product containing all six xylenol isomers that is sold in the greatest volume and that contains the highest percentage of xylenol isomers is WES 297. This

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[1] For the same reason, as discussed in Merisol's concurrently submitted proposal for ethylphenols, isolation of all pure m- and p-ethylphenols by distillation is not possible. Isolation of the o-ethylphenol isomer by distillation is possible, but has not proved to be commercially viable.

[2] Merisol is selling quantities of 3,4-xylenol that total 16,000 pounds, well below the HPV 1 million pound threshold. This 16,000 pounds is a portion of a 35,000 pound batch toll produced in Europe for Merisol more than three years ago as a developmental project.

[3] Merisol has imported 3,5-xylenol in quantities less than 1 million pounds per year for use in its mixtures and has imported 35,000 pounds of 3,4-xylenol (see footnote 2). Merisol understands that one other company may have imported 2,4-xylenol in quantities over 1 million pounds per year in 1999, 2000, and 2001 and that this quantity was used as an intermediate in the production of another substance. Less than 350,000 pounds of pure 2,5-xylenol have been imported into the U.S. in 2000 and 2001. Merisol understands that small amounts (<20,000 pounds per year) of pure 2,3-xylenol may have been imported into the U.S. in 2000 and 2001.

product contains 22.5% xylenols, the highest percentage in any Merisol product containing xylenol isomers.

Table : Distribution of Individual Xylenol Isomers
In Merisol Products

	Number of Different Xylenol Isomers Present as Components In Merisol Products					
	1 xylenol isomer in product*	2 xylenol isomers in product	3 xylenol isomers in product	4 xylenol isomers in product	5 xylenol isomers in product	6 xylenol isomers in product
% of total xylenol placed into commerce by Merisol	0.7	34.7	2.3	0.6	34.0	27.5

* 2,6-xylenol is the xylenol in the product (SIDS dossier available for this isomer).

Exposure to xylenols, then, is primarily to a mixture of xylenol isomers. Accordingly, Merisol has developed HPV data for the Mixed Xylenols Category using a mixture of the xylenol isomers.

DESCRIPTION OF THE CATEGORY

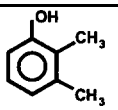
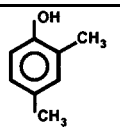
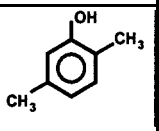
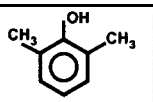
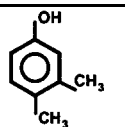
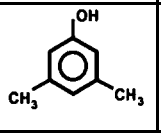
Mixed Xylenols

Each of the xylenol isomers (and an entity called "mixed xylenols") appears in the EPA HPV list of chemicals to be evaluated. Identification of the isomers is presented in Text Table 2, below. Although a CAS Registry Number has been assigned to "mixed xylenols," and mixed xylenols has been included as a test substance in the HPV Chemical Challenge Program, no definition of mixed xylenols (CAS# 1300716) is available, nor is there a single product or mixture understood by industry as "mixed xylenols." For purposes of establishing the, test mixture for the Mixed Xylenols Category, Merisol defines mixed xylenols as a mixture containing portions of xylenol isomers normalized to match the ratios of xylenol isomers occurring in the actual Merisol commercial product containing the highest percentage of all six xylenols, WES 297. The composition of the Mixed Xylenols Test Mixture is:

Xylenol isomer	Mole % in Test Mixture
2,5-xylenol (CAS# 95874)	16.4
3,4-xylenol (CAS# 95658)	16.9
2,4-xylenol (CAS# 105679)	22.7
3,5-xylenol (CAS# 108689)	11.1
2,3-xylenol (CAS# 526750)	18.2
2,6-xylenol (CAS# 576261)	14.7.

This mixture mimics worker and consumer exposure to the highest percentage of xylenols contained in an actual commercial product, but allows for the study of xylenol isomers without confounding effects of non-xylenol product components It represents the Category "Mixed Xylenols" for HPV data development, as well as each separate xylenol isomer. Each isomer is represented in the Category. Data developed on this Category are intended to represent all mixtures of xylenols, as well as the individual xylenol isomers.

Table 2: Xylenols – Chemical Name, CAS Number, and Structure

Chemical:	2,3-Xylenol	2,4-Xylenol	2,5-Xylenol	2,6-Xylenol	3,4-Xylenol	3,5-Xylenol
CAS Registry Number	526750	105679	95874	576261	95658	108689
Molecular structure						

CATEGORY JUSTIFICATION

Mixed Xylenols

As structural isomers, the members of the Mixed Xylenols Category share the same molecular weight, or in the case of the mixture, average molecular weight. The substituent groups on the phenolic ring are always methyl groups, so branching differences among the side groups is not a possibility in this Category. Examination of the physical-chemical properties for each isomer (Text Table 3) shows that the physical-chemical properties of the isomers are quite similar, due to the structural similarities. Of particular importance to environmental effects and potential human health effects are the values for octanol/water partition coefficient and water solubility. The values for octanol/water partition coefficient are 2.33 to 2.42 for each of the xylenols. Water solubility values at 25°C are reported to range from 3540 mg/L to 7870 mg/L. These values suggest that xylenol isomers and mixtures of isomers will distribute similarly in the environment and have similar residence times in environmental compartments. Bioaccumulation attributes will be similar among the isomers and the mixture also. Vapor pressures of the isomers at 25°C range from 0.04 to 0.27 mmHg for the xylenols, also supporting a similar pattern of airborne distribution. Individually and as a group the xylenols are expected to exhibit low-to-moderate mobility in soil based on the $K_{o/w}$ values. Hydrolysis values have not been reported for xylenols, presumably due to the absence of a hydrolyzable functional group. Within the family of xylenol isomers, the physicochemical properties will manifest similar effects on the environment and potentially on human health.

The biological response patterns of xylenols, like the physicochemical properties, derive from the structural similarities of the isomers. There are data from independent sources to support this position by way of example or illustration. For instance, in work completed by the National Toxicology Program (NTP) with a group of structurally-related isomers, in this case methyl phenols, or cresols, toxicology studies showed that there was no one predominantly toxic isomer and that target organs for toxicity and toxic effect dose levels were relatively consistent

across the isomers. New data summarized in this submission show that this is also the case for xylenols.

Table 3: Xylenols Physical Properties

Chemical	2,3-Xylenol	2,4-Xylenol	2,5-Xylenol	2,6-Xylenol	1 3,4-Xylenol	13,5-Xylenol
CAS Registry Number	526750	105679	95874	57626 1	95658	108689
Boiling Point	216.9°C	211.0°C	211.2°C	201.1°C	227.0°C	221.7°C
Melting Point	72.6°C	24.5°C	74.8°C	45.6°C	62.1°C	63.4°C
Octanol/Water Partition Coefficient	2.42	2.36	2 . 3 6	2.36	2.33	2.35
Water Solubility	4750 mg/L @ 25°C	7870 mg/L @ 25°C	3540 mg/L @ 25°C	6050 mg/L @ 25°C	4760 mg/L @ 25°C	4880 mg/L @ 25°C
Vapor Pressure	0.09mmHg@ 25°C	O.llmmHg@ 25°C	0.16mmHg@5 ° C	0.27mmHg@ 25°C	0.04mmHg@ ° C	.0.04mmHg@ 25°C
Biodegradation	Complete in unacclimated soil 19 days	Unacclimated soil $T_{1/2}$ = 3.5days	Complete in activated sludge 5 days	Complete in acclimated soil 5-14 days	Complete in unacclimated soil 9 days	Complete in unacclimated soil 11 days
Photodegradation in Air	$T_{1/2}$ = 4.8 hrs	$T_{1/2}$ = 5.3 hrs	$T_{1/2}$ = 4.8 hrs	$T_{1/2}$ = 5.8 hrs	$T_{1/2}$ = 4.7 hrs	$T_{1/2}$ = 3.4 hrs

NA = Not Availat e

Evaluation of New and Existing Mammalian Toxicitv. Genetic Toxicitv and Ecotoxicity Data for Xylenols

a. Mammalian Acute and Repeated-Dose Toxicity

Mammalian toxicity testing of 2,6-xylenol, the most thoroughly tested isomer, is limited. The acute oral LD_{50} is most reliably reported as 1470 mg/kg. Values of 296-1750 mg/kg are reported for rats and other species (SIDS, 1997). Acute dermal penetration (LD_{50}) studies have been completed in rats, mice and rabbits and the resulting LD_{50} values range from 920 to over 2325 mg/kg (SIDS, 1997). The acute inhalation LC_{50} in rats is reported to be >270 mg/m^3 for a 4-hour exposure, and 2,6-xylenol is reported to be a strong skin and eye irritant (SIDS, 1997). The results were negative in a Guinea pig study for dermal sensitization (SIDS, 1997).

Rodent oral LD_{50} values for other xylenol isomers from unpublished reports (or secondary source reports) are: 444 mg/kg, 400 mg/kg, 2300 mg/kg, and 608 mg/kg for 2,5-, 3,4-, 2,4- and 3,5- xylenol, respectively. The lack of detail presented in the study reports and possible

overall quality of these reports should be considered when comparisons are made about comparability of acute toxicities across isomers. The most reliable report for a rat acute oral LD_{50} value is the 2005 study of the Mixed Xylenols Test Mixture, which produced an LD_{50} of 980.62 mg/kg. The study design for this work was the "Up and Down" method, which is intended to reduce test animal utilization but which also reduces the number of dose levels evaluated. Accordingly, the LD_{50} value from a study of this design may not reflect mortality experience seen from a broader dosing range. This could account for some of the difference between mean lethal values reported for xylenol isomers and for the Mixed Xylenols Test Mixture. Given methodological differences in acute lethality determinations and the inherent imprecision of the endpoint value calculation, these results for acute rodent lethality do not provide a basis for excluding 960 mg/kg as representative of the Mixed Xylenols Category. Indeed, the 960 mg/kg value is representative of the Mixed Xyenols Category if for no other reason than as a measured value 960 mg/kg is close to the mean of rat oral LD50 values reported for xylenol isomers (1205 mg/kg).

Repeated-dose toxicity has been studied for 2,6-xylenol. In oral gavage studies ranging from 28 days to 10 months with rats and in one case, mice, 2,6-xylenol produced damage to the liver and glandular stomach (28-day study) and to the liver, spleen, heart and kidney (lo-month study). Rats tolerated 100 mg/kg/day for shorter-term exposures (28 days). According to a translation of the Russian work, the LOAEL for a lo-month study was 6 mg/kg/day and the NOAEL was reported to be 0.06 mg/kg/day (SIDS, 1997). Although of shorter duration, the 28-day study is presented in Table 4 instead of the lo-month study because of the greater reliability that can be assigned to the study report. Support for the Category comes from the most reliable studies of repeated-dose toxicity across the isomers, the 90-day study on 2,4-xylenol and the 28-day study on 2,6-xylenol. These provide NOAEL values that are quite similar: 50 mg/kg/day in the 90-day study and something between 20-100 mg/kg/day in the 28-day study. The authors of the 28-day study reported separate NOAEL values by test animal sex. A simple average, although not strictly justified, would be 60 mg/kg/day, which compares well to the 90-day NOAEL for 2,4-xylenol.

Further support for the Mixed Xylenols Category can be found in the results of current repeat-dose testing in rats of the Mixed Xylenols Test Mixture, which produced an oral (gavage) NOAEL of 100 mg/kg/day. Dosing was for 28 days in male rats and 54 days in female rats. Because dose levels were 30, 100, and 245 mg/kg/day, the real NOAEL falls somewhere between 30 and 100 mg/kg/day for each sex. These values are not dissimilar from those published for the xylenol isomers. Since little systemic toxicity was seen in the study, the LOAEL was based on clinical signs in males and females and organ weight changes (kidney, liver, ovaries) in females.

At dose levels and durations common to specific isomer testing (2,4-xylenol and 2,6-xylenol) and with Mixed Xylenols Test Mixture testing, very little, if any, differences were observed in toxicologic response. At doses below 245 mg/kg/day for 54 days or less, 2,4-xylenol produced no changes in mice and 2,6-xylenol and the Mixed Xylenols Test Mixture each produced absolute and relative increases in rat liver weight. The Mixed Xylenols Test Mixture also produced an increase in female relative kidney weight but none of the test substances, single isomer or mixture, produced gross or microscopic changes in any organ or tissue, including those

organs exhibiting weight change. At higher oral dose levels or for dosing beyond 54 days, stomach ulceration has been reported. Thus, NOAELs for those xylenol isomers, which have been evaluated in repeated-dose oral toxicity studies in rodents and the Mixed Xylenols Test Mixture, all fall in the range of 20-100 mg/kg/day. This demonstrates that there is no important toxicological difference in repeated-dose systemic toxicity among isomers of xylenol and that the Mixed Xylenols Category adequately represents xylenol isomers.

b. Reproductive and Develonmental Toxicitv

There are no reports of reproductive toxicity studies conducted with any xylenol. An oral gavage developmental toxicity study in rats has recently been completed with the 2,6 isomer. The NOAEL for developmental toxicity was 180 mg/kg/day, based on reduction in fetal weight. The NOAEL for maternal toxicity was 60 mg/kg/day based on body weight gain suppression and decreased food consumption (SIDS, 1997).

Reproductive toxicity/developmental toxicity screening of the Mixed Xylenols Test Mixture produced a reproductive/developmental NOAEL of 100 mg/kg/day based on reduced mating frequency at the next highest dose level of 245 mg/kg/day. At maternally toxic doses, neither the 2,6-isomer or the Mixed Xylenols Test Mixture produced effects on implantation sites, number of still born pups, pup viability, sex ratio, and, importantly, neither caused pup mortality or malformation. This pattern of low or no developmental or reproductive toxicity, even in the presence of parental systemic toxicity, is consistent with the absence of an isomer effect and supports utilization of Mixed Xylenols Test Mixture results as representative of the Category.

c. Genetic Toxicitv

Each of the xylenol isomers, except 3,5-xylenol, has been evaluated in bacterial mutation tests usually with two (TA98 and TA 100) Salmonella strains. 2,6-Xylenol was tested with four strains. The work was completed with and without exogenous metabolic activation, and was negative for gene mutation. Most of this work is published. When tested in five bacterial strains, the Mixed Xylenols Test Mixture was negative for mutation in the Ames bacterial mutation test both in the presence and absence of exogenous metabolic activation.

2,6-Xylenol is reported to be negative for gene mutation in bacterial and mammalian cell assays, with and without exogenous metabolic activation (SIDS, 1997). ***In vitro*** cytogenetics testing with V79 cells produced signs of chromosomal aberration; ***in*** vivo testing (rat bone marrow, oral gavage) was negative for chromosome effects, including aberration (SIDS, 1997).

Just as the 2,6-isomer did in V79 cells, the Mixed Xylenols Test Mixture produced structural and numeric chromosome aberrations when tested in Chinese hamster ovary cells grown in culture and tested with and without exogenous metabolic activation.

In vitro genetic toxicity testing of xylenol isomers and the Mixed Xylenols Test Mixture produced essentially identical results and has done so when subjected to rodent metabolic activation. This strongly suggests that the inherent activity of xylenol isomers is

indistinguishable in these test systems. These results also strongly suggest that rat liver Phase I metabolism products of the isomers are indistinguishable in these assays.

d. Environmental Toxicity and Environmental Fate

The acute aquatic environmental toxicity of the xylenols has been characterized in several marine and freshwater fish and invertebrate species using static and flowthrough exposure procedures. The EC_{50} values issuing from these studies range from 3 to 53 mg/L for fish and 2.1 to 16.5 mg/L for Daphnia. These values are from unpublished studies or secondary sources.

Acute 4-hour testing of Daphnia with the Mixed Xylenols Test Mixture produced an immobilization LC_{50} of 7.7 mg/L (5.4-11 mg/L). This value is very much in line with acute Daphnia toxicity values reported for xylenol isomers.

An acute algal toxicity test has been completed on 2,6-xylenol. The LC_{50} was reported as 325 mg/L, a value distinctly different from the acute Daphnia LC_{50} and acute fathead minnow LC_{50} reported for the same compound (11 and 27 mg/L, respectively). This value for the algal LC_{50} is also inconsistent with the Mixed Xylenols Test Mixture acute algal LC_{50} of 14 mg/L based on biomass. Algal tests with 2,6-xylenol and with the Mixed Xylenols Test Mixture both used static exposures but the Mixed Xylenols Test Mixture test employed a covered vessel to control test material loss due to volatilization. Analysis for test material concentration in algal cultures was not performed in testing of 2,6-xylenol (it was performed with the Mixed Xylenols Test Mixture), so loss of test material from test culture for any reason would not be detected and would not be taken into account when reporting nominal test concentrations. This fact alone could explain any difference in acute algal LC_{50} values between 2,6-xylenol and the Mixed Xylenols Test Mixture. Beyond this there is a strong concordance among acute aquatic toxicity test results for xylenol isomers and the Mixed Xylenols Test Mixture. This supports use of the Mixed Xylenols Category as a surrogate for individual xylenol isomers testing.

Biodegradation of each of the xylenol isomers has been investigated and reported. Aerobic and anaerobic degradation studies from several environmental media (activated and unactivated soils, sludge and sediments) indicate that complete degradation of each isomer occurs in less than 21 days (the half-life for 2,4-xylenol in unacclimated soil was 3.5 days). Accordingly, xylenols are readily biodegraded in the environment.

There is potential for the direct photolysis of each of the xylenol isomers, since an absorption band extends over 290 nm and the xylenols may absorb light in the environmental *W* spectrum. The manufacture and use pattern for xylenols does not afford significant opportunity for *W* light exposure, so the importance of this mechanism for degradation would be limited to spills of the xylenols or xylenol-containing products. In air, xylenols are relatively photolytic with photolysis half-lives of less than 6 hours.

Table 4: Xylenols Category Data Matrix

	Acute mammalian toxicity	Repeat dose toxicity	Gene tox (point mutat)	Gene tox (chromosome)	Repro-tox	Develop-ment tox	Acute fish tox	Acute daphnia tox	Algal tox	Biodeg
2,5-xylenol	Rat oral 444 mg/kg	ND	Neg Ames	ND	ND	ND	EC_{50} = 3-5 mg/L	EC_{50} = 10 mg/L	ND	Readily biodegradable See Table 3
3,4-xylenol	Mouse oral 400 mg/kg	ND	Neg Ames	N D	ND	ND	EC_{50} = 15 mg/L	ND	N D	Readily biodegradable See Table 3
2,4-xylenol	Rat oral 2300 mg/kg	3-month oral mouse NOAEL 50 mg/kg/day	Neg Ames	N D	ND	ND	EC_{50} = 17 mg/L	EC_{50} = 2.1 mg/l	ND	Readily biodegradable See Table 3
3,5-xylenol	Rat oral 608 mg/kg	ND	N D	N D	ND	ND	EC_{50} = 53 mg/L	ND	N D	Readily biodegradable See Table 3
2,3-xylenol	Mouse iv LD_{50} 56 mg/kg	ND	Neg Ames	N D	N D	N D	N D	EC_{50} = 16 mg/L	N D	Readily biodegradable See Table 3
2,6-xylenol	Rat oral 1470 mg/kg	28-day rat oral NOAEL 20 mg/kg/day for female 100mg/kg/day for males	Neg Ames	Neg *In vivo* Rat NOAEL >1400 mg/kg/day	N D	Rat Maternal NOAEL 60 mg/kg Devel NOAEL 180 mg/kg	EC_{50} = 27 mg/L	EC_{50} = 11mg/L	LC_{100} 325 mg/L	Readily biodegradable See Table 3
Mixed Xylenols	Rat oral 980 mg/kg	28-day oral – males; 54-day oral females NOAEL = 100 mg/kg/day	Neg Ames	Positive *In Vitro* Structural and numeric aberrations	Repro/develop NOAEL = 100 mg/kg/day		ND	EC_{50} = 7.7 mg/L	Biomass EC_{50} = 14 mg/L Growth EC_{50} >22 mg/L	ND

ND = No Data

Toxicological Justification for the Mixed Xylenols Category

Xylenols are dimethyl phenols, and there is experience with methyl phenols that illustrates and supports Merisol's Mixed Xylenols Category for HPV data generation. The toxicological justification for the Mixed Xylenols Category is that existing studies of structurally related compounds, methyl phenols (also known as cresols), have demonstrated that the methyl phenol isomers are remarkably equivalent in toxicity and that binary and tertiary mixtures of cresol isomers do not produce toxic interactions among the isomers, i.e., that mixtures of cresol isomers do not exhibit more than additive toxicity.[4] More importantly, existing studies on mixed xylenols or its isomers, and newly conducted studies by Merisol with the Mixed Xylenols Test Mixture, as discussed further below, also support the toxicological justification of this Category. Initially we. described the cresols data below because they provide a cogent illustration of a Structure-Activity-Relationship across an isomeric series. A relationship of this type is now demonstrated with Xylenol isomers and we believe that the xylenol isomers act analogously based on their similar chemical/physical properties. For purposes of clarity. we do not believe that cresol data apply directly to mixed xylenols with regard to HPV testing requirements, and we do not present these data for that purpose.

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[4] In 28-day feeding studies conducted on cresol isomers by the NTP, mice and rats were treated with equivalent dose levels of each isomer and in 90-day studies rats received equivalent doses of ortho-cresol or the meta/para-mix. The author of the study, Dennis Dietz, observed so little difference among the cresol isomers in toxicity (both concentration and dose effects) that he chose to summarize the results of the 28- and 90-day studies together. In summarizing the subchronic toxicity of cresol isomers, Dietz said:

> The cresol isomers exhibited a generally similar pattern of toxicities in rats and mice. Dietary concentrations of 3,000 ppm appeared to be minimal effect levels for increases in liver and kidney weights and 15,000 ppm for deficits in liver function. Histopathologic changes, including bone marrow hypocellularity, irritation to the gastrointestinal tract and nasal epithelia, and atrophy of female reproductive organs, occasionally occurred at 10,000 ppm, but were more common at the high dose of 30,000 ppm (Ref. NTP, 1992).

In these studies, which included an assessment of individual isomers and an isomer mix, no evidence of toxic interaction was reported by the author, Dietz. In the final report of those studies, Dietz concluded that "In summary, the various cresol isomers exhibited a generally similar spectrum of toxicities in these studies, with few exceptions as noted previously. There was little evidence to suggest a significant increase in toxicity with longer exposures in the 13-week study when compared to the effects seen with similar doses in the 28-day study."

Evaluation of Cresols Data

Attachment 1 to this document presents in tabular form summaries of developmental and reproductive toxicity data, as well as genetic toxicity data on methyl phenol isomers. From inspection of the Attachment 1 tables, it can be seen that within a test animal species (rabbit or rat), methyl phenol (cresol) isomers exhibited similar or the same toxicity. Effective doses, expressed as NOAELs, remained constant or very close across isomers, never more than one dose level apart. Target organs for isomer toxicity and systemic toxic effects were nearly superimposable across isomers. This qualitative and quantitative comparability of toxicity across isomers exhibited in the cresols data set is consistent with cresol isomers results described by Dennis Deitz, cited in the footnote above. Genetic toxicity studies of the cresol isomers show few inconsistencies in test results across isomers. In the seven cases where there are data on a mixture of the isomers, as well as data on one or more isomers, there is no difference in results in those cases (two) where data are available on each isomer and the mixture. In another case, the positive assay result for the mixture can be attributed to a positive result for an isomer in the same test. In the remaining four examples, isomeric uniformity of genetic activity cannot be affirmed or refuted because of the incomplete data set.

The toxicological equivalence or near equivalence of methyl phenols (cresols) derives from the structural similarity shared by members of the group (isomeric forms of methyl phenol) and the similarity in chemical/physical properties which follows from the structural relationship. In an analogous manner, a complementary structure-activity relationship was shown with dimethyl phenols (xylenol isomers) based on the structural similarity among this group of isomers. The demonstration of a structure-activity relationship among the methyl phenol isomers and the parallel structure-activity relationship for the homolog dimethyl phenols is the toxicological justification of the Mixed Xylenols Category for HPV testing.

CATEGORY TEST PLAN

From inspection of Table 4, it can be seen that where complementary data exist on isomers, a concordance in results is apparent. Merisol notes that only a portion of the testing on 2,6-xylenol (some in mammalian cell *in vitro* mutation work, *in vivo* cytogenetics, and the developmental toxicity study) was conducted and reported under GLP conditions. Many details for the remainder of the work on xylenols are unavailable. Thus, while the existing mammalian and ecological toxicology data, when viewed as a whole, strongly support toxicology data development on a xylenol mixture as a category for HPV testing, the data may not in every case be adequately reported to be relied upon for HPV evaluations.

Merisol believes that submitted data for physiochemical properties, photodegradation, biodegradation, and toxicity to fish and invertebrates are sufficient for addressing these endpoints for the HPV Challenge Program. As noted in previous versions of this test plan, Merisol has not performed hydrolysis testing, which is not appropriate for these substances, and is not determining fugacity endpoint, which is fulfilled by modeling and cannot be run appropriately with mixtures. Accordingly, Merisol has only conducted the studies listed in Table 5 using the Mixed Xylenols Test Mixture (composition shown below) to supply data for SIDS endpoints in the Mixed Xylenols Category.

Xylenol isomer	Mole % in Test Mixture
2,5-xylenol (CAS# 95874)	16.4
3,4-xylenol (CAS# 95658)	16.9
2,4-xylenol (CAS# 105679)	22.7
3,5-xylenol (CAS# 108689)	11.1
2,3-xylenol (CAS# 526750)	18.2
2,6-xylenol (CAS# 576261)	14.7.

This mixture represents the Category "Mixed Xylenols" for HPV data development, as well as each separate xylenol isomer. Data developed on this Category are intended to satisfy all requirements under the HPV Challenge Program for all mixtures of xylenols, as well as the individual xylenol isomers.

CONCLUSION

Xylenol mixtures sold or distributed in the U.S. by Merisol are of variable composition. Testing every possible variation would have violated animal use goals without producing additional meaningful scientific information, and would thus also would have been unnecessarily burdensome. Because exposure of people and the environment is primarily to mixtures of xylenols, data were developed on a mixture of six xylenols and those data (Table 5) have provided cogent and reliable information for assessment of the potential hazards that xylenol-containing products may present to humans and the environment. This approach to data development accounts for any interactions between xylenol isomers that may impact toxicity.
The consistency of these results across endpoints establishes that within the isomeric family of xylenols there are no important toxicological differences and that data developed on the Mixed Xylenols Test Mixture adequately characterize each isomer of xylenol. Similarity of endpoint NOAELs on a variety of endpoints derived in a variety of dosing regimes, dose-response characteristics, and target organs all support the assertion that xylenols do not exhibit any important isomeric effect in toxicity. Because of this, Merisol believes that all members of the Mixed Xylenols Category have equivalent general toxicity and that separate testing of isomers is not required.

Table 5: Mixed Xylenols Category HPV Test Plan

HPV DATA ENDPOINT	PROPOSED DATA DEVELOPMENT METHOD	TESTING RESULTS
1. HEALTH EFFECTS		
Acute Toxicity	Acute Oral Toxicity: OECD Health Effects Test Guideline 425	The Acute oral LD_{50} = 980.62 mg/kg and the NOAEL = 175 mg/kg at post-dose 14
Repeat-Dose Toxicity	Combined Repeat-Dose Toxicity Study with Reproductive/Developmental Toxicity Screen: OECD Health Effects Test Guideline 422	The NOAEL for systemic toxicity was 100 mg/kg/day because of clinical observations and organ weight changes at the highest dose (urine-stained fur; increased kidney, liver and ovarian relative weight)
Repro-Develop. Toxicity		The reproductive NOAEL was 100 mg/kg/day due to reduced mating at 245 mg/kg/day
Genetic Toxicity	Bacterial Mutation Test: OECD Health Effects Test Guideline 471	The test material was negative for mutation in the presence and absence of exogenous metabolic activation
	In vitro chromosomal aberration test OECD Guideline 473	The percentage of cells with structural aberrations (but not numeric) was significantly increased by 4-hour treatment with mixed xylenols in the presence of exogenous metabolic activation; the percentage of cells with numeric (but not structural) aberrations was significantly increased by 4-hour treatment with mixed xylenols in the absence of exogenous metabolic activation; 20-hour exposure produced an increase in structural but not numeric aberrations
2. ECOTOXICITY		
Daphnia	Acute Toxicity to Aquatic Invertebrates: OECD Test Guideline 202	Immobilization of daphnids The 48-hour EC_{50} = 7.7 mg/L (5.4 11 mg/L) 48-hour growth rate NOEC = 5.4 mg/L
Algae	Acute Toxicity to Aquatic Plants (Algae): OECD Test Guideline 20 1	Total biomass EC_{50} = 14 mg/l (12- 15 mg/L) 72-hour biomass NOEC = 1.7 mg/L Growth rate EC_{50} >22 mg/L 72-hour growth rate NOEC = 1.7 mg/L

REFERENCES

NTP Report on the Toxicity Studies of Cresols in F344/N Rats and B6C3F1 Mice. Dennis Dietz, US Department of Health and Humans Services, February, 1992.

Reduced SIDS Dossier: 2,6-Dimethylphenol, CAS Number 576-26-2, Sponsor Country USA, September 2, 1997.

ATTACHMENT 1

Mammalian reproductive/developmental toxicity summaries and genetic toxicity summaries of methyl phenol isomers (o-, m-, and p-cresol)

.

CRESOLS ISOMER MAMMALIAN TOXICITY COMPARISON

STUDY NOAEL	o-CRESOL	m-CRESOL	p-CRESOL
Rabbit Oral Gavage Developmental Toxicity: Maternal NOAEL & Effect/Target Organ	NOAEL = 5 mg/kg/day Maternal LOAEL = 50 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes.	NOAEL = 5 mg/kg/day Maternal LOAEL = 50 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes.	Maternal NOAEL = 5 mg/kg/day Maternal LOAEL = 50 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes; 15% and 35% mortality in mid- and high-dose vs. 0% in controls.
Rabbit Oral Gavage Developmental Toxicity: Developmental NOAEL & Effect/Target Organ	Developmental NOAEL = 50 mg/kg/day No embryotoxicity or fetotoxicity. Skeletal variations observed in high-dose pups (100mg/kg/day)	Developmental NOAEL= 100 mg/kg/day No embryotoxicity or fetotoxicity.	Developmental NOAEL = 100 mg/kg/day No embryotoxicity or fetotoxicity.
Rat Oral Gavage Developmental Toxicity: Maternal NOAEL & Effect/Target Organ	Maternal NOAEL 175 mg/kg/day Maternal LOAEL = 450 mg/kg/dayHypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 16% mortality.	Maternal NOAEL = 175 mg/kg/day Maternal LOAEL = 450 mg/kg/day Hypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 0% mortality.	Maternal NOAEL = 175 mg/kg/day Maternal LOAEL = 450 mg/kg/day. Hypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 12% mortality.
Rat Oral Gavage Developmental Toxicity: Developmental NOAEL & Effect/Target Organ	Developmental NOAEL = 175 mg/kg/day No increase in malformations, visceral variations at the high-dose.	Developmental NOAEL= 450 mg/kg/day No increase in malformations. No increase in variations.	Developmental NOAEL = 175 mg/kg/day No increase in malformations, skeletal variations at the high-dose.
Two-Generation Reproductive Toxicity in Rats by Oral Gavage: Parental NOAEL & Effect/Target Organ	Parental NOEAL 30 mg/kg/day Parental LOAEL = 175 mg/kg/day. Transient hypoactivity, audible respiration, ataxia, twitches, tremors, initially decreased food consumption and body weight gain, 52%-28% mortality across sexes and generations. No lesions specifically noted in organs from FO and F 1 adult necropsy.	Parental NOAEL <30 mg/kg/day Effects included high-dose mortality (450mg/kg/day). Transient hypoactivity, audible respiration, ataxia, twitches, tremors, initially decreased food consumption and body weight gain, 40%-12% mortality across sexes and generations. Brain hemorrhage, atrophied seminal vesicle, lung congestion noted at necropsy of FO and F1 parents.	Parental NOAEL = 30 mg/kg/day Parental LOAEL = 175 mg/\kg/day. High-dose mortality (450 mg/.kg/day). Transient hypoactivity, audible respiration, ataxia, twitches, tremors, initially decreased food consumption and body weight gain, 40%-4% mortality across sexes and generations. Lung congestion noted at necropsy of FO parents, atrophied seminal vesicle and lung congestion noted at necropsy of F1 parents.
Two-Generation Reproductive Toxicity in Rats by Oral Gavage: Offspring NOAEL & Effect/Target Organ	F1 and F2 NOAEL = 175 mg/kg/day No gross lesions in F1 or F2 pups.	F1 and F2 NOAEL = 175 mg/kg/day No gross lesions in F1 or F2 pups.	F1 and F2 NOAEL = 175 mg/kg/day No gross lesions in F1 or F2 pups.

SUMMARY OF CRESOLS MUTAGENICITY DATA

ASSAY	TEST SUBSTANCE			
GENE MUTATION	ORTHO	META	PARA	MIXED
SALMONELLA ACTIVATION	-	-	-	-
SALMONELLA NONACTIVATION	-	-	-	-
MOUSE LYMPHOMA ACTIVATION	-	nd	nd	+
MOUSE LYMPHOMA NONACTIVATION	-	nd	nd	nd
*MOUSE LYMPHOMA ACTIVATION	nd			nd
*MOUSE LYMPHOMA NONACTIVATION	nd			nd
*SLRL DROSOPHILA		nd		nd
DNA EFFECTS				
UDS		nd	+	+
*HEPATOCYTE UDS	nd	-	nd	nd
CHROMOSOME DAMAGE				
ROOT TIP	+	+	+	nd
SCE ACTIVATION	?	-	-	+
SCE NONACTIVATION	?	-	-	+
*CHO CYTOGENETICS ACTIVATION	+		+	nd
*CHO CYTOGENETICS NONACTIVATION	+		+	nd
*MOUSE (IN VIVO) CYTOGENETICS	nd	-	nd	nd
*MOUSE DOMINANT LETHAL	-	nd	-	nd
MOUSE MICRONUCLEUS				-
CELL TRANSFORMATION				
BALB/C 3T3 ACTIVATION	-	nd	nd	+
*BALB/C 3T3 ACTIVATION	-	-	nd	nd
*BALB/C 3T3 NONACTIVATION	nd	-	+	nd
C3H10T1/2 ACTIVATION	nd	nd	+	nd
C3H10T1/2 NONACTIVATION	nd	nd	nd	nd

* ACC PANEL ASSAYS

nd = No Test Data
+ = Positive for Genetic Toxicity
- = Negative for Genetic Toxicity
? = Equivocal Results for Genetic Toxicity

REFERENCES: ATTACHMENT 1

Developmental Toxicity and Reproductive Toxicity References:

R. W. Tyl, Unpublished Report Number 5 l-508: "Developmental Toxicity Evaluation of o-, m-, or p-cresol Administered by Gavage to New Zealand White Rabbits," Bushy Run Research Center, Export, Pa., June 27, 1988.

R. W. Tyl, Unpublished Report Number 5 l-509: "Developmental Toxicity Evaluation of o-, m-, or p-cresol Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., June 29, 1988.

T. L. Neeper-Bradley and R. W. Tyl, R. W. Tyl, Unpublished Report Number 5 l-634: "Two Generation Reproduction Study of m-Cresol, Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., February 28, 1989.

T. L. Neeper-Bradley and R. W. Tyl, R. W. Tyl, Unpublished Report Number 51-614: "Two Generation Reproduction Study of o-Cresol, Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., December 19, 1989.

T. L. Neeper-Bradley and R. W. Tyl, R. W. Tyl, Unpublished Report Number 5 l-5 12: "Two Generation Reproduction Study of p-Cresol, Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., March 28, 1989.

Genetic Toxicitv References:

IUCLID Data Sheet: o-Cresol CAS Number 95-48-7, European Chemicals Bureau, February 11, 2000.

IUCLID Data Sheet: m-Cresol CAS Number 103-39-4, European Chemicals Bureau, June 19, 1997.

IUCLID Data Sheet: Mixed Cresols CAS Number 13 19-77-3, European Chemicals Bureau, March 1,200 1.

APPENDIX A
ROBUST SUMMARIES FOR MIXED XYLENOLS STUDIES SUPPORTING THE MIXED XYLENOLS CATEGORY

Algal toxicity

TEST SUBSTANCE	Xylenols Isomer Mixture	Mole % in Test Mixture
Identity	2,5-Xylenol (CAS) 95-87-4	16.4
	3,4-Xylenol (CAS) 95-65-8	16.9
CAS #	2,4-Xylenol (CAS) 105-67-9	22.7
	3,5-Xylenol (CAS) 108-68-9	11.1
	2,3-Xylenol (CAS) 526-75-O	18.2
	2,6-Xylenol (CAS) 576-26-l	14.7
Remarks	Test substance was a mixture of xylenol isomers blended as indicated above. Lot number 20NOV2003 99.74% purity	
METHOD		
Method/guideline	OECD Guideline 201 Alga, Growth Inhibition Test (OECD, 1984) Static, acute	
GLP	Yes	
Year	***2005***	
Species	***Psuedokirchnerielle subcapitata***	
Analytical monitoring	Yes, GC/FID analysis on samples collected at 0 and 72 hours	
Exposure period	72 hours	
Statistical methods	**Yes**	
Test conditions	Closed system, 72-hour duration, temperature range 22-24°C, continuous illumination at 7000 to 8600 lux (650 to 800 footcandles), shaking rate 100 rpm. Triplicate algal cultures Used for each treatment level. Five treatment levels, negative, solvent and three analytical QC control groups. Test exposure levels were based on pilot testing; actual test concentrations were 0, 1.7, 3.1, 6.3, 13 and 25 mg/L. pH was 8.2 at study initiation and 8.9 to 9.5 at 72 hours. Cell number was measured at 24, 48, and 72 hours.	
RESULTS		
Concentration	0, 1.7, 3.1, 6.3, 13 and 25 mg/L Mean measured	
Endpoint criteria	Inhibition of total biomass (area under growth curve) and average growth rate relative to control	
EC_{50}	Total biomass EC_{50} = 14 mg/l (12- 15 mg/L) 72-hour biomass NOEC = 1.7 mg/L Growth rate EC_{50} >22 mg/L 72-hour growth rate NOEC = 1.7 mg/L	
DATA QUALITY		

Reliability	(1) Reliable without restrictions
REFERENCES	Mixed Xylenols Acute Toxicity to the Freshwater Green Alga, *Psuedokirchneriella subcapitata.*, Springborn Smithers Laboratory Report 13824.6101, Wareham, MA. June 7, 2005

Daphnia toxicity

TEST SUBSTANCE	Xylenols Isomer Mixture	Mole % in Test Mixture
Identity	2,5-Xylenol (CAS) 95-87-4	16.4
	3,4-Xylenol (CAS) 95-65-8	16.9
CAS #	2,4-Xylenol (CAS) 105-67-9	22.7
	3,5-Xylenol (CAS) 108-68-9	11.1
	2,3-Xylenol (CAS) 526-75-O	18.2
	2,6-Xylenol (CAS) 576-26-l	14.7
Remarks	Test substance was a mixture of xylenol isomers blended as indicated above. Lot number 20NOV2003 99.74% purity	
METHOD		
Method/guideline	OECD Guideline 202 Daphnia sp. Acute Immobilization Test (OECD, 1984) Static, acute	
GLP	**Yes**	
Year	2005	
Species	*Daphnia magna*	
Analytical monitoring	Yes, GC/FID analysis on samples collected at 0 and 48 hours	
Exposure period	48 hours	
Statistical methods	**Yes**	
Test conditions	Closed system, 48-hour duration, temperature range 19-2 1 "C. Four replicate vessels with five daphnids each were used for each treatment level. Five treatment levels, negative, solvent and three analytical QC control groups. Test exposure levels were based on pilot testing; actual test concentrations were 0, 2.0, 5.4, 11, 21 and 47 mg/L. pH was 8.0 at study initiation. Specific conductance was 500 µmhos/cm; total hardness (as $CaCO_3$) was 190 mg/L total alkalinity (as $CaCO_3$) was 120 mg/L. Preliminary testing indicated that volatilization of mixed xylenols test material could be controlled with closed test vessels.	
RESULTS		
Concentration	0, 2.0, 5.4, 11, 21 and 47 mg/L Mean measured	
Endpoint criteria	Immobilization of daphnids	

EC50	The 48-hour EC_{50} = 7.7 mg/L (5.4 – 11 mg/L) 48-hour growth rate NOEC = 5.4 mg/L
DATA QUALITY **Reliability**	(1) Reliable without restrictions
REFERENCES	Mixed Xylenols Acute Toxicity to the Water Fleas, *Duphnia magna,* Under Static Conditions. Springborn Smithers Laboratorv Report 13824.6102. Wareham. MA. June 7.2005

Bacterial Mutation Test

TEST SUBSTANCE	Xylenols Isomer Mixture — Mole % in Test Mixture
Identity	2,5-Xylenol (CAS) 95-87-4 — 16.4
	3,4-Xylenol (CAS) 95-65-8 — 16.9
CAS #	2,4-Xylenol (CAS) 105-67-g — 22.7
	3,5-Xylenol (CAS) 108-68-g — 11.1
	2,3-Xylenol (CAS) 526-75-O — 18.2
	2,6-Xylenol (CAS) 576-26-l — 14.7
Comments	Test substance was a mixture of xylenol isomers blended as indicated above. Lot number 20NOV2003 99.74% purity
METHOD	
Method/guideline	OECD Guideline 47 1 Bacterial Reverse Mutation Test
Type	Plate incorporation with and without exogenous metabolic activation (Aroclor 1254-induced rat liver *S-9) five Salmonella typhimurium* strains (TA 98, TA 100, TA1535, TA 1537) and *Escherichia coli WP2* uvrA
GLP	Yes
Year	2004
Analytical monitoring	No
Exposure period	48-72 hours
Statistical methods	Mean and Std Dev of revertant counts
Test conditions	Preliminary testing included test material solubility and cytotoxicity (dose range finding). Condition of background lawn prior was evaluated prior to mutagenicity testing. Test, positive and negative control cultures were plated in triplicate. DMSO was used as a solvent for the test material. Five test concentrations ranging from 50 to 5000 µg/plate were evaluated.
RESULTS	
Concentration	75, 200, 600, 1800 and 5000
Units	µg test material/plate
Conclusion	Toxicity as observed at 1800 and 5000 µg/plate. No test

	material precipitation was observed. The test material was negative for mutation in the presence and absence of exogenous metabolic activation.
DATA QUALITY **Reliability**	(1) Reliable without restrictions
REFERENCES	Bacterial Reverse Mutation Assay: Mixed Xylenols. BioReliance Laboratory, Rockville, Md., Study Number AA89JJ.502.BTL, November 1, 2004.

In Vitro Mammalian Chromosome Aberration Test

TEST SUBSTANCE	Xylenols Isomer Mixture	Mole % in Test Mixture
Identity	2,5-Xylenol (CAS) 95-87-4	16.4
	3,4-Xylenol (CAS) 95-65-8	16.9
CAS #	2,4-Xylenol (CAS) 105-67-9	22.7
	3,5-Xylenol (CAS) 108-68-9	11.1
	2,3-Xylenol (CAS) 526-75-O	18.2
	2,6-Xylenol (CAS) 576-26-l	14.7
Comments	Test substance was a mixture of xylenol isomers blended as indicated above. Lot number 20NOV2003 99.74% purity	
METHOD		
Method/guideline	OECD Guideline 473 Mammalian Cell Chromosome Aberration Test; Evans, et al. (1976) Cytological methods for detecting chemical mutagens, in A. Hollaender (Ed.) Chemical Mutagens, Principles and Methods for their detection, Vo1.4, Plenum Press, NY.; Galloway, et al., (1994) Report from working group on *in vitro* tests for chromosome aberrations, Mutation Research 3 12 (3): 241-246 Chinese hamster ovary (CHO) cells with and without exogenous metabolic activation (Aroclor 1254-induced male rat liver S-9) evaluated for numerical and structural aberration	
GLP	Yes	
Year	2004	
Analytical monitoring	No	
Exposure period	Non-activated cultures: 4 and 20 hours; activated cultures: 4 hours	
Statistical methods	Number and types of chromosome aberrations scored and	

	analyzed using Fisher's exact test and, if positive in the Fisher's test, Co&ran-Armitage test was used to measure dose-responsiveness.
Test conditions	Preliminary testing included test material solubility and cytotoxicity (nine concentrations) with and without S-9. Test, positive and negative control cultures were cultured in duplicate. DMSO was used as a solvent for the test material. Three-to-eight test concentrations were employed depending on exposure time (4 or 20 hours) or presence or absence of S-9. Mitotic index was determined to ensure adequate number of metaphase cells. A minimum of 200 metaphase spreads were examined for chromatid and chromosomal structural or numerical aberrations. Chromatid gaps were scored but not included in analysis.
RESULTS **Conclusion**	Based on cell growth inhibition at test material concentrations ≥1500 µg/mL in S-9 activated and nonactivated 4-hour cultures and ≥500 µg/mL in the nonactivated 20-hour cultures, test dose levels were: 37.5 - 1200 µg/mL for S-9 activated and nonactvated 4-hour exposures and 12.5 - 600 µg/mL for 20-hour exposures. Additional testing for activated and nonactivated 4-hour cultures was conducted at 75, 150, 300, 350, 400, 450, 400, 550 and 600 µg/mL. The percentage of cells with structural aberrations (but not numeric) was significantly increased by 4-hour treatment with mixed xylenols in the presence of exogenous metabolic activation; the percentage of cells with numeric (but not structural) aberrations was significantly increased by 4-hour treatment with mixed xylenols in the absence of exogenous metabolic activation. 20-Hour exposure produced an increase in structural but not numeric aberrations.
DATA QUALITY **Reliability**	(1) Reliable without restrictions
REFERENCES	Mammalian Chromosome Aberration Test: Mixed Xylenols. BioReliance Laboratory, Rockville, Md., Study Number AA89JJ.33 1 .BTL, November 3, 2004.

Mammalian acute toxicity

TEST SUBSTANCE **Identity**	Xylenols Isomer Mixture	Mole % in Test Mixture
	2,5-Xylenol (CAS) 95-87-4	16.4
	3,4-Xylenol (CAS) 95-65-8	16.9

CAS #	2,4-Xylenol (CAS) 105-67-9 22.7 3,5-Xylenol (CAS) 108-68-9 11.1 2,3-Xylenol (CAS) 526-75-O 18.2 2,6-Xylenol (CAS) 576-26-l 14.7
Remarks	Test substance was a mixture of xylenol isomers blended as indicated above. Lot number 20NOV2003 99.74% purity
METHOD	
Method/guideline	OECD Guideline 425, Acute Oral Toxicity -- Up and Down Procedure (December 200 1) Acute oral gavage
GLP	**Yes**
Year	2005
Species	Female Sprague-Dawley rat
Analytical monitoring	**Yes**
Exposure period	Single exposure, 14-day post-exposure observation period
Statistical methods	Yes, averages and proportions calculated on body weight gain and survival
Test conditions	Single, oral gavage dosing of test material to overnight fasted rats. Corn oil was the vehicle. Animals observed for clinical observations (7 times daily on day of dosing) and viability (twice daily), body weight and food consumption were recorded daily, gross necropsy at sacrifice.
RESULTS	
Concentration	175,550 or 1750 mg/kg
Endpoint criteria	Mortality Nine animals were tested. Mortality occurred in five animals; one in the mid-dose and four in the high-dose groups. Clinical observations included hunched posture, excess salivation in the mid- and top-dose group. High-dose animals developed decreased motor activity, twitching behavior, lacrimation, prostration, ptosis, ataxia, impaired righting reflexes and limb use, and hyperpnea. Signs developed rapidly following dosing and disappeared by day 2 post-dosing. Weight-gain was reduced in the mid-dose group only.
LD_{50}	The acute oral LD_{50} = 980.62 mg/kg and the NOAEL = 175 mg/kg at post-dose 14.
DATA QUALITY	
Reliability	(1) Reliable without restrictions
REFERENCES	Acute Oral Toxicity Study of Mixed Xylenols in Rats -- Up and Down Procedure. CR-DDS Argus Division Report 3713-001, Horsham, PA., March 16, 2005

Mammalian repeated-dose toxicity
Reproductive/developmental toxicity

TEST SUBSTANCE **Identity** **CAS #** **Remarks**	Xylenols Isomer Mixture — Mole % in Test Mixture 2,5-Xylenol (CAS) 95-87-4 — 16.4 3,4-Xylenol (CAS) 95-65-8 — 16.9 2,4-Xylenol (CAS) 105-67-9 — 22.7 3,5-Xylenol (CAS) 108-68-9 — 11.1 2,3-Xylenol (CAS) 526-75-O — 18.2 2,6-Xylenol (CAS) 576-26-l — 14.7 Test substance was a mixture of xylenol isomers blended as indicated above. Lot number 20NOV2003 99.74% purity
METHOD **Method/guideline** **GLP** **Year** **Species** **Analytical monitoring** **Exposure period** **Statistical methods** **Test conditions**	 OECD Guideline 422, Combined Repeated-Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test (March 1996) Repeated-dose, oral gavage Yes 2005 Female Sprague-Dawley rat Yes, GC/FID analysis of dosing preparation concentration, stability and homogeneity. 28 days for males; 54 days for females Yes, body weight, weight gains and reproductive endpoints analyzed by ANOVA and Dunnett's. Reproductive data analyzed by Fisher's exact. Ten adult male and 10 female rats per group, three test and one control group, received test material or vehicle orally by gavage daily for at leas 28 days (males) or 54 days (females). Dosing before and during mating, during gestation and for days l-5 of lactation. Observations for viability, clinical signs of toxicity, food consumption and body weight gain, functional observational battery and motor activity, hematology, clinical chemistry, developmental toxicity and reproductive performance, gross and microscopic post-mortem examination
RESULTS **Concentration** **Endpoint criteria**	 0, 30, 100 or 245 mg/kg/day Systemic toxicity in adult male and female rats; reproductive performance; developmental toxicity, neurotoxicity. All rats survived treatment. In males, urine staining of fur was seen at the highest treatment level. Body weight gain and food consumption was unaffected

	by treatment. Mating frequency was reduced at the top dose level, 245 mg/kg/day. Neurotoxicity (motor activity and FOB) was not produced by treatment; there were no treatment-related effects seen at gross necropsy or histopathologically. In females, urine staining of fur was seen at the high dose level. Body weight gain and food consumption during pre-mating, mating, gestation and lactation were unaffected by treatment. Mating and fertility were unaffected by treatment. Pup viability was unaffected by treatment. F1 animals showed no clinical or necropsy signs related to treatment of pregnant dams. Neurotoxicity (motor activity and FOB) was not produced by treatment; there were no treatment-related effects seen at gross necropsy or histopathologically, although relative weights of kidney, liver and ovaries were increased in the high-dose group
NOAEL	The NOAEL for the study was 100 mg/kg/day because of clinical observations and organ weight changes at the highest dose (urine-stained fur; increased kidney, liver and ovarian relative weight). The reproductive NOAEL was >245 mg/kg/day due to reduced mating at 245 mg/kg/day.
DATA QUALITY **Reliability**	(1) Reliable without restrictions
REFERENCES	Oral (gavage) Combined Repeated-Dose Toxicity Study of Mixed Xylenols and Ethyl Phenols with the Reproductive/Developmental Toxicity Screening Test. CR-DDS Argus Division Report 37 13-003, Horsham, PA., November 22, 2005

(1) Klimisch, H. J., M. Andreae, and U. Tillmann. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regulatory Toxicol. and Pharmacol. 25:1-5.

APPENDIX B
ROBUST SUMMARIES FOR 2,3-XYLENOL STUDIES SUPPORTING THE MIXED XYLENOLS CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
2,3-Xylenol (CAS 526-75-O)

Type	: Melting Point
Value	: 72.56 °C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: unknown
GLP	: unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980, plus additional literature references.

Type	: Boiling Point
Value	: 216.92 °C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: Unknown
GLP	: unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980, plus additional literature references.

Type	: Vapor Pressure
Value	: 0.09 mmHg at 25°C
Method	: Calculated from vapor pressure constants in reference
GLP	: Unknown
Year	: Unknown
Remarks	: None
Quality	: Estimated < 3% error

Reliability : (2) Reliable with restrictions

(3): Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR values regressed from three literature references.

Type : Partition Coefficient
Value : Log Kow = 2.42
Method : Unknown
GLP : unknown
Year : Unknown
Remarks : Reference's Log Kow for other xylenols slightly high vs. other sources.
Quality : Unknown
Reliability : (2) Reliable with restrictions

(4) Lu, et. al., "Quantitative Relationship Study for the Structure and Biodegradability of Substituted Benzenes", *Chemical Journal on the Internet*, Vol. 3, No. 1, 2001.

Type : Water Solubility
Value : *4750* mg/L @ 25°C
Method : Uknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(5) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : pKa Value
Value : 10.54 @ 25°C
Method : Unknown
GLP : unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(6) : Ullmann's Encyclopedia of Industrial Chemistry (1985), Vol. A8, p. 48

ECOTOXICITY ELEMENTS
2,3-Xylenol (CAS 526-75-O)

Type : Atmospheric fate
Value : T1/2 = 4.8 hours
Method : Structure activated method

GLP	: Unknown
Y e a r	: 1993
Remarks	: Vapor-phase 2,3-xylenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles Reaction rate constant = 8.02x10S-11 cc/molecule-set @ 25°C
Quality	: unknown
Reliability	: (4) Not Assignable

(7) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Soil aerobic degradation
Value	: 100% removal in 19 days
Method	: Incubation with carbonaceous wood loam soil @ 19°C
GLP	: Unknown
Year	: 1981
Remarks	: Laboratory study
Quality	: unknown
Reliability	: (4) Not Assignable

(8) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aerobic activated sludge degradation
Value	: 99% removal
Method	: Dissolved air treatment degradation simulator
GLP	: Unknown
Year	: 1982
Remarks	: Laboratory study
Quality	: unknown
Reliability	: (4) Not Assignable

(9) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aqueous aerobic degradation
Value	: Below detection level in 14 days
Method	: Contaminated groundwater water in shake flask
GLP	: Unknown
Year	: 1991
Remarks	: Laboratory study
Quality	: unknown
Reliability	: (4) Not Assignable

(10) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

MAMMALIAN TOXICOLOGY ELEMENTS
2,3-Xylenol (CAS 526-75-O)

Type	: Acute
Species	: Mouse
Sex	: Not stated
Strain	: Not stated
Route of administration	: Intravenous
Exposure period	:NA
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: Not stated
Control group	: Not stated
LC50	: 56 mg/kg
Method	:Not stated .
Year	: 1996
GLP	: No
Test substance	: 2,3-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(11) Lewis, R. J., Sax's Dangerous Properties of Industrial Materials. 9" edition. p 3405, Van Nostrand, New York, 1996.

GENETIC TOXICITY IN VITRO
2,3-Xylenol (CAS 526-75-O)

Type	: Ames test
System of testing	: Salmonella typhimurium TA 98 and TA 100
Test concentration	: Not stated
Metabolic activiation	: Not stated'
Result	: Negative for mutagenicity
Year	: 1979
Test substance	: Purity not stated
GLP	: No information
Remark	: Work appears to have been conducted on shale oil products and derivatives
Reliability	: (3) Not Reliable

(12) Epler, J. L., et al. Environ Health Persp., 30: 179-184, 1979.

ECOTOXICITY ELEMENTS
2,3-Xylenol (CAS 526-75-O)

Type	: Acute
Species	: Daphnia magna
Sex	: Not applicable
Strain	: Not applicable
Route of administration	: static bioassay
Exposure period	: 48 hr
Frequency of treatment	: One day
Post exposure period	: Not applicable
Doses	: Not stated
Control group	: Not stated
LC50	: 16.0 mg/l
Method	: Not stated
Year	: 1975
GLP	: Not stated
Test substance	: 2,3-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(13) Grushko, Y, et al., Hydrobiological J., 11 (5) 93-99, 1975.

APPENDIX C
ROBUST SUMMARIES FOR 2,4-XYLENOL STUDIES SUPPORTING THE MIXED XYLENOLS CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
2,4-Xylenol (CAS 105-67-9)

Type	: Melting Point
Value	: 24.53 °C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: Unknown
GLP	: unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) Revised 200 1, DIPPR value taken from Texas A&M Thermodynamics Research Center "Key Chemical Data Books – Xylenols", 1978.

Type	: Boiling Point
Value	: 210.98 °C
Decomposition	: No
Sublimation	: No
Method	: unknown
Year	: unknown
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) Revised 200 1, DIPPR value taken from Texas A&M Thermodynamics Research Center "Key Chemical Data Books – Xylenols", 1978.

Type	: Vapor Pressure
Value	: 0.11 mmHg at 25°C
Method	: Calculated from vapor pressure constants in reference
GLP	: Unknown
Year	: unknown
Remarks	: None
Quality	: Estimated < 3% error
Reliability	: (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) Revised 2001, DIPPR values regressed from four literature references.

Type	: Partition Coefficient
Value	: Log Kow = 2.36
Method	: Unknown
GLP	: Unknown
Year	: Unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(4) National Library of Medicine Hazardous Substances. Data Base; May 8, 2002

Type	: Log Kow
Value	: 2.42
Method	: Unknown
GLP	: unknown
Year	: Unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(5): Verschueren, "Handbook of Environmental Data on Organic Chemicals"

Type	: Water Solubility
Value	: 7870 mg/L @ 25°C
Method	: Uknown
GLP	: unknown
Year	: unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(6): National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: pKa Value
Value	: 10.60 @ 25°C
Method	: Unknown
GLP	: unknown
Year	: unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(7) : Ullmann's Encyclopedia of Industrial Chemistry (1985), Vol. A8, p. 48

ENVIRONMENTAL FATE ELEMENTS
2,4-Xylenol (CAS 105-67-9)

Type	: Atmospheric fate
Value	: T1/2 = 5.3 hours
Method	: Structure activated method
GLP	: Unknown
Year	: 1993
Remarks	: Vapor-phase 2,4-xylenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles Reaction rate constant = 7.20x1 OS- 11 cc/molecule-set @ 25°C
Quality	: unknown
Reliability	: (4) Not Assignable

(8) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Soil aerobic degradation
Value	: T1/2 in unacclimated soil = 3.5 days
Method	: Incubation with unacclimated soil @ 19°C
GLP	: Unknown
Year	: 1989
Remarks	: Laboratory study
Quality	: unknown
Reliability	: (4) Not Assignable

(9) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Contaminated soil aerobic degradation
Value	: T1/2 in contaminated soil = 248 days
Method	: incubation with soil from manufactured gas plant
GLP	: Unknown
Year	: 1993
Remarks	: Laboratory study
Quality	: Unknown
Reliability	: (4) Not Assignable

(10) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aerobic activated wastewater degradation
Value	: 42.8% reduced BOD after 10 days
Method	: Biological treatment simulator
GLP	: Unknown
Year	: 1990
Remarks	: Laboratory study
Quality	: unknown

Reliability : (4) Not Assignable

(11) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aqueous aerobic degradation
Value	: Below detection level in 14 days
Method	: Contaminated groundwater water in shake flask
GLP	: Unknown
Year	: 1991
Remarks	: Laboratory study
Quality	: Unknown
Reliability	: (4) Not Assignable

(12) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

MAMMALIAN TOXICOLOGY ELEMENTS
2,4-Xylenol (CAS 105-67-g)

Type	: Acute
Species	: Rat
Sex	: Not stated
Strain	: Not stated
Route of administration	: Oral
Exposure period	:NA
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: Not stated
Control group	: Not stated
LD50	: 2300 mg/kg
Method	: Not stated
Year	: 1996
GLP	: No
Test substance	: 2,4-Dimethyl xylenol, purity not stated
Reliability	(4) Not assignable

(13) Lewis, R. J., Sax's Dangerous Properties of Industrial Materials. 9" edition. p 3405, Van Nostrand, New York, 1996.

Type	: Acute
Species	: Mouse
Sex	: Not stated
Strain	: Not stated
Route of administration	: Oral
Exposure period	:NA
Frequency of treatment	: One day
Post exposure period	: Not stated

Doses	: Not stated
Control group	: Not stated
LC50	: 809 mg/kg
Method	: Not stated
Year	: 1996
GLP	: No
Test substance	: 2,4-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(14) Lewis, R. J., Sax's Dangerous Properties of Industrial Materials. 9th edition. p 3405, Van Nostrand, New York, 1996.

Type	: Subchronic
Species	: Mouse
Sex	: 30 male and 30 female per group
Strain	: Not stated
Route of administration	: Oral gavage
Exposure period	: 90 days
Frequency of treatment	: One day
Post exposure period	: None
Doses	: 5.0, 50.0 or 250.0 mg/kg/day
Control groups	: (2) untreated and vehicle
NOAEL	: 50 mg/kg/day
Results	: No treatment-related changes in survival or body weight, food consumptuon or eye examination. High-dose clinical signs and hematological changes in females (decreased corpuscular Hb and cell volume). No gross or microscopic changes, no organ weight changes except increase in low-dose adrenal weights (females).
Year	: 1989
GLP	: No
Test substance	: 2,4-Dimethyl xylenol, purity not stated
Reliability	: (1) Reliable without restriction

(15) US EPA Ninety-day gavage study in albino mice using 2,4-dimethylphenol. Study number 410-2831, 1989.

GENETIC TOXICITY IN VITRO
2,4-Xylenol (CAS 105-67-g)

Type	: Ames test
System of testing	: Salmonella typhimurium TA97, TA 8, TA 00, TA1535 and TA 537
Test concentration	: 0.33, 1.0, 3.3, 10 and 33µg/plate
Metabolic activiation	: With and without rat or hamster S-9
Result	: Negative for mutagenicity

Year	: 1986
Test substance	: Purity not stated
GLP	: No information
Remark	: None
Reliability	: (1) Reliable without restriction

(16) Mortlemans, K., Environ Mutagenesis 8, l-l 19, 1986.

ECOTOXICITY ELEMENTS
2,4-Xylenol (CAS 105-67-9)

Type	: Acute
Species	: Fathead minnow
Sex	: Not stated
Strain	: Not applicable
Route of administration	: Flow-through
Exposure period	: 96 hr
Frequency of treatment	: One day
Post exposure period	: Not applicable
Doses	: 0, 5.2, 8.6, 14.4, 24.0 and 40.0 mg/l, analytical verification
Control group	: Untreated
LC50	: 16.6 mg/l
Method	: Evaluate test water quality, fish behavior and pharmacotoxic signs, body weight and survival.
Year	: 1985
GLP	: Not stated
Test substance	: 2,4-Dimethyl xylenol, purity not stated
Reliability	: (2) Reliable with restrictions

(17) Geiger, D. L., et al., Acute toxicities of organic chemicals to fathead minnows, Vol. II. Center for Lake Superior Environmental Studies, U. of Wisconsin – Superior. US EPA Cooperative Agreements Superior, WI., p 185, 1985.

Type	: Acute
Species	: Daphnia magna
Sex	: Not applicable
Strain	: Not applicable
Route of administration	: static bioassay
Exposure period	: 48 hr
Frequency of treatment	: One day
Post exposure period	: Not applicable
Doses	: Not stated
Control group	: Not stated
LC50	: 2.1 mg/l
Method	: Not stated

Year	: 1980
GLP	: Not stated
Test substance	: 2,3-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(18) US EPA Ambient Water Quality Criteria Doc., 2,4-dimethylphenol. EPA Document 440/5-80-044, p B-l, 1980.

APPENDIX D
ROBUST SUMMARIES FOR 2,5-XYLENOL STUDIES SUPPORTING THE MIXED XYLENOLS CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
2,5-Xylenol (CAS 95-87-4)

Type	: Melting Point
Value	: 74.84 °C
Decomposition	: No
Sublimation	: No
Method	: unknown
Year	: unknown
GLP	: unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR value taken from Texas A&M Thermodynamics Research Center "Key Chemical Data Books – Xylenols", 1978, plus two other sources.

Type	: Boiling Point
Value	: 211.18 °C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: unknown
GLP	: unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR value taken from Texas A&M Thermodynamics Research Center "Key Chemical Data Books – Xylenols", 1978, plus two other sources.

Type	: Vapor Pressure
Value	: 0.16 mmHg at 25°C
Method	: Calculated from vapor pressure constants in reference
GLP	: unknown
Year	: Unknown
Remarks	: None
Quality	: Estimated < 3% error
Reliability	: (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR values regressed from three literature references.

Type : Partition Coefficient
Value : Log Kow = 2.36
Method : Unknown
GLP : unknown
Year : unknown
Remarks : None
Quality : unknown
Reliability : (2) Reliable with restrictions

(4): National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : Water Solubility
Value : 3540 mg/L
Method : Uknown
GLP : unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(5): National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : pKa Value
Value : 10.60
Method : Unknown
GLP : unknown
Year : unknown
Remarks : None
Quality : unknown
Reliability : (2) Reliable with restrictions

(6) Ullmann's Encyclopedia of Industrial Chemistry (1985), Vol. A8, p. 48

ENVIRONMENTAL FATE ELEMENTS
2,5-Xylenol (CAS 95-87-4)

Type : Atmospheric fate
Value : T1/2 = 4.8 hours
Method : Structure activated method
GLP : Unknown
Year : 1993
Remarks : Vapor-phase 2,5-xylenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles

Reaction rate constant = 4.00x10S-11 cc/molecule-set @ 25°C
Quality : Unknown
Reliability : (4) Not Assignable

(7) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : Soil aerobic degradation
Value : 100% removal in 19 days
Method : Incubation with carbonaceous wood loam soil @ 19°C
GLP : Unknown
Year : 1981
Remarks : Laboratory study
Quality : unknown
Reliability : (4) Not Assignable

(8) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : Aqueous aerobic degradation
Value : Below detection level in 14 days
Method : Contaminated groundwater water in shake flask
GLP : Unknown
Year : 1991
Remarks : Laboratory study
Quality : Unknown
Reliability : (4) Not Assignable

(9) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : Aerobic activated sludge degradation
Value : 94.5% reduced BOD after 5 days
Method : Biological treatment simulator
GLP : Unknown
Year : 1976
Remarks : Laboratory study
Quality : unknown
Reliability : (4) Not Assignable

(10) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

MAMMALIAN TOXICOLOGY ELEMENTS
2,5-Xylenol (CAS 95-87-4)

Type : Acute
Species : Rat
Sex : Not stated

Strain	: Not stated
Route of administration	: Oral
Exposure period	:NA
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: Not stated
Control group	: Not stated
LC50	: 444 mg/kg
Method	: Not stated
Year	: 1996
GLP	: No
Test substance	: 2,4-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(11) Lewis, R. J., Sax's Dangerous Properties of Industrial Materials. 9th edition. p 3405, Van Nostrand, New York, 1996.

Type	: Acute
Species	: Mouse
Sex	: Not stated
Strain	: Not stated
Route of administration	: Oral
Exposure period	:NA
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: -Not stated
Control group	: Not stated
LC50	: 385 mg/kg
Method	: Not stated
Year	: 1996
GLP	: No
Test substance	: 2,4-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(12) Lewis; R. J., Sax's Dangerous Properties of Industrial Materials. 9" edition. p 3405, Van Nostrand, New York, 1996.

Type	: Acute
Species	: Rabbit
Sex	: Not stated
Strain	: Not stated
Route of administration	: Oral
Exposure period	:NA
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: Not stated

Control group	: Not stated
LC50	: 938 mg/kg
Method	: Not stated
Year	: 1996
GLP	: No
Test substance	: 2,4-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(13) Lewis, R. J., Sax's Dangerous Properties of Industrial Materials. 9th edition. p 3405, Van Nostrand, New York, 1996.

GENETIC TOXICITY IN VITRO
2,5-Xylenol (CAS 95-87-4)

Type	: Ames test
System of testing	: Salmonella typhimurium TA 98 and TA 100
Test concentration	: Not stated
Metabolic activiation	: Not stated
Result	: Negative for mutagenicity
Year	: 1979
Test substance	: Purity not stated
GLP	: No information
Remark	: Work appears to have been conducted on shale oil products and derivatives
Reliability	: (3) Not Reliable

(14) Epler, J. L., et al. Environ Health Persp., 30: 179-184, 1979.

ECOTOXICITY ELEMENTS
2,5-Xylenol (CAS 95-87-4)

Type	: Acute
Species	: Rainbow trout
Sex	: Not applicable
Strain	: Not applicable
Route of administration	: Static bioassay
Exposure period	: 96 hr
Frequency of treatment	: One day
Post exposure period	: Not applicable
Doses	: Not stated
Control group	: Not stated
LC50	: 3.2-5.6 mg/l
Method	: Not stated
Year	: 1983
GLP	: Not stated
Test substance	: 2,3-Dimethyl xylenol, purity not stated

Reliability : (4) Not assignable

(15) Verschueren, K. Handbook of Enviromnentakl Data of Organic Chemicals, 2nd edition. New York, Van Nostrand, p 1196, 1983.

Type	: Acute
Species	: Daphnia magna
Sex	: Not applicable
Strain	: Not applicable
Route of administration	: static bioassay
Exposure period	: 48 hr
Frequency of treatment	: One day
Post exposure period	: Not applicable
Doses	: Not stated
Control. group	: Not stated
LC50	: 10.0 mg/l
Method	: Not stated
Year	: 1975
GLP	: Not stated
Test substance	: 2,3-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(16) Grushko, Y, et al., Hydrobiological J., 11 (5) 93-99, 1975.

APPENDIX E
ROBUST SUMMARIES FOR 2,6-XYLENOL STUDIES SUPPORTING THE MIXED XYLENOLS CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
2,6-Xylenol (CAS 576-26-l)

Type	: Melting Point
Value	: 45.61 °C
Decomposition	: No
Sublimation	: No
Method	: unknown
Year	: Unknown
GLP	: unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR value taken from Texas A&M Thermodynamics Research Center "Key Chemical Data Books – Xylenols", 1978, plus two other sources.

Type	: Boiling Point
Value	: 201.07 °C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: Unknown
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR value taken from Texas A&M Thermodynamics Research Center "Key Chemical Data Books – Xylenols", 1978, plus two other sources.

Type	: Vapor Pressure
Value	: 0.27 mmHg at 25°C
Method	: Calculated from vapor pressure constants in reference
GLP	: unknown
Year	: Unknown
Remarks	: None
Quality	: Estimated < 3% error
Reliability	: (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR values regressed from four literature references.

Type	: Partition Coefficient
Value	: Log Kow = 2.36
Method	: unknown
GLP	: unknown
Year	: Unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(4): National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Log Kow
Value	: 2.36
Method	: unknown
GLP	: Unknown
Year	: Unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(5) Verschueren, "Handbook of Environmental Data on Organic Chemicals"

Type	: Water Solubility
Value	: 6050 mg/L @ 25°C
Method	: Uknown
GLP	: unknown
Year	: Unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(6) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: pKa Value
Value	: 10.63
Method	: unknown
GLP	: unknown
Year	: Unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(7) Ullmann's Encyclopedia of Industrial Chemistry (1985), Vol. A8, p. 48

ENVIRONMENTAL FATE ELEMENTS
2,6-Xylenol (CAS 576-26-l)

Type	: Atmospheric fate
Value	: T1/2 = 5.8 hours
Method	: Structure activated method
GLP	: unknown
Year	: 1993
Remarks	: Vapor-phase 2,6-xylenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles. Reaction rate constant = 6.60x10S-11 cc/molecule-set @ 25°C
Quality	: unknown
Reliability	: (4) Not Assignable

(8) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Soil-sludge aerobic degradation
Value	: 94.3% COD after 5 days
Method	: Incubation with activated sludge seed
GLP	: unknown
Year	: 1976
Remarks	: Laboratory study
Quality	: unknown
Reliability	: (4) Not Assignable

(9) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aqueous aerobic degradation
Value	: Below detection level in 14 days
Method	: Contaminated groundwater water in shake flask
GLP	: unknown
Year	: 1991
Remarks	: Laboratory study
Quality	: Unknown
Reliability	: (4) Not Assignable

(10) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aerobic degradation in adapted inoculum
Concentration	: 200 mg/L in water
Degradation	: 94% (exposure time not stated)
Test material analysis	: measurement of COD
GLP	: Not stated
Test Material	: 2,6-Dimethyl xylenol, purity not stated
Reliablility	: (4) Not assignable

(11) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 18, 1997.

MAMMALIAN TOXICOLOGY ELEMENTS
2,6-Xylenol (CAS 576-26-l)

Type	: Acute
Species	: Rat
Sex	: males, S/group
Strain	: Not stated
Route of administration	: Oral
Exposure period	:NA
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: **100, 215, 464, 1000, 21**50 or 4640 **mg/kg**
Control group	: Not stated
LC50	: 1470 **mg/kg**
Method	: Not stated
Results	: No mortality below **1000mg/kg;** clinical signs included depression, exophthahnos, flushing, salivation, ataxia and prostration
Year	: 1996
GLP	: **No**
Test substance	: **2,6-Dimethyl** xylenol, purity not stated
Reliability	: (4) Not assignable

(12) SIDS Dossier **2,6-Dimethylphenol**. Sponsor Country USA, **p.** 25, 1997.

Type	: Acute
Species	: Rat
Sex	: males, S/group
Strain	: Not stated
Route of administration	: Oral
Exposure period	:NA
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	:**100, 215, 464, 1000, 2150** or 4640 **mg/kg**
Control group	: Not stated
LC50	: 1470 **mg/kg**
Method	: Not stated
Results	: No mortality below **1000mg/kg;** clinical signs included depression, exophthahnos, flushing, salivation, ataxia and prostration
Year	: 1996
GLP	: **No**
Test substance	: **2,6-Dimethyl** xylenol, purity not stated
Reliability	: (4) Not assignable

(13) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 26, 1997.

Type	: Acute
Species	: Rat
Sex	: Number, sex not tstated
Strain	: Not stated
Route of administration	: Inhalation
Exposure period	: 4 hours
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: Not tstated
Control group	: Not stated
LC50	: >270 mg/m^3
Method	: Not stated
Results	: Signs included agitation, labored breathing, spasms
Year	: Not stated
GLP	: Not stated
Test substance	: 2,6-Dimethyl xylenol, purity not stated
Reliability	: (3) Not reliable

(14) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 29, 1997.

Type	: Acute
Species	: Rat
Sex	: Number, sex not stated
Strain	: Not stated
Route of administration	: Dermal
Exposure period	:NA
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: Not stated
Control group	: Not stated
LD50	: 1500 mg/kg
Method	: Not stated
Results	: No details provided
Year	: 1970
GLP	: No
Test substance	: 2,6-Dimethyl xylenol, purity not stated
Reliability	: (3) Not reliable

(15) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 30, 1997.

Type	: Skin irritation
Species	: Rabbit
Sex	: 6 (3 intact, 3 abraded)
Strain	: Not stated

Route of administration	: Non-occlusive
Exposure period	: Not stated
Frequency of treatment	: Not stated
Post exposure period	: 24 and 72 hours
Doses	: 0.5 g undiluted
Control group	: Not stated
Result	: Corrosive, caused severe burns
Method	: Not stated
Year	: 1965
GLP	: No
Test substance	: 2,6-Dimethyl xylenol, purity not stated
Reliability	: (2) Reliable with restrictions

(16) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 33, 1997.

Type	: Eye irritation
Species	: Rabbit
Sex	: Not stated, 6 test animals
Strain	: Not stated
Route of administration	: Instillation into conjunctival sac of one eye
Exposure period	: Not stated
Frequency of treatment	: One day
Post exposure period	: 24, 48 and 72 hours
Doses	: 100 mg
Control group	: Each animal served as own control
Method	: Not stated
Results	: Severe irritation, cornea1 opacity, cornea1 sloughing. Cornea1 damage in all test animals at 72 hours
Year	: 1965
GLP	: No
Test substance	: 2,6-Dimethyl xylenol, purity not stated
Reliability	: (2) Reliable with restrictions

(17) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 34, 1997.

Type	: Skin sensitization
Species	: Guinea pig
Sex	: Albino, sex and number not stated
Strain	: Not stated
Route of administration	: Dermal
Exposure period	: Single dose
Post exposure period	: 13 days followed by challenge
Doses	: Not stated
Control group	: Not stated
Result	: Not a sensitizer
Method	: Modified Landsteiner

Year	: 1965
GLP	: No
Test substance	: 2,6-Dimethyl xylenol, purity not stated
Reliability	: (2) Reliable with restrictions

(18) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 36, 1997.

Type	: Subchronic
Species	: Rat
Sex	: 56 males; assignment to groups not stated
Strain	: Not stated
Route of administration	: Oral gavage
Exposure period	: 8 months
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: 0.06 or 6.0 mg/kg/day
Control groups	: untreated
NOAEL	: 0.06 mg/kg/day
Results	: High-dose produced reductiuon in body weight and decrease in SH groups in blood serum. Hypotension reported for high-dose animals. Microscopic changes reported in high-dose liver, spleen, kidney and heart. Statistical analysis not reported.
Year	: 1968
GLP	: No
Test substance	: 2,6-Dimethyl xylenol, purity not stated
Reliability	: (3) Not reliable; details lacking – questionable translation from Russian literature.

(19) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 39, 1997.

Type	: Subchronic
Species	: Rat
Sex	: 5 males 5 females per group
Strain	: Wistar
Route of administration	: Oral gavage
Exposure period	: 28 days
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: 20, 100, 400 and 800 mg/kg/day
Control groups	: untreated
NOAEL	: 20mg/kg/day for females; 100 mg/kg/day for males
Results	: Increased liver weight (absolute and relative) in 100 mg/kg/day females and both sexes at higher doses. Ulceration of stomach at 400mg/kg/day and above along with anemia and histological changes in spleen.

Year	: 1993
GLP	: Yes
Test substance	: 2,6-Dimethyl xylenol, purity >99.9%
Reliability	: (1) Reliable without restriction.

(20) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 37, 1997.

GENETIC TOXICITY IN VITRO
2,6-Xylenol (CAS 576-26-l)

Type	: Ames test
System of testing	: Salmonella typhimurium TA 98, TA 100, TA 1535 and TA 1537
Test concentration	: 10.0, 33.3, 100.0, 333.3, 1000.0, 2500.0 and 5000.0 µg/plate
Metabolic activiation	: With and without S-9
Result	: Negative for mutagenicity
Year	: 1994
Test substance	: Purity >98.9%
GLP	: No information
Remark	: None
Reliability	: (1) Reliable without restriction

(21) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 43, 1997.

GENETIC TOXICITY IN VIVO
2,6-Xylenol (CAS 576-26- 1)

Type	: Bone marrow cytogenetics
Species	: Rat
Sex	: 15 males and 15 females per group (except high-dose – 20 per sex)
Strain	: SD
Route of administration	: Oral gavage
Exposure period	
Frequency of treatment	: Not stated; OECD method 475
Post exposure period	: 36 hours
Doses	: 0, 350, 700 and 1400 mg/kg/day for males; 0, 300, 600 and 1200 mg/kg/day for females
Control groups	: untreated and positive
NOAEL	: for males; 1200 mg/kg/day for males
Results	: Bone marrow cells collected at 12, 24 and 36 hours post dosing. Examination for structural and numeric chromosome aberrations. No statistical increase in aberrations in treated groups verses control.
Year	: 1996

GLP	: Yes
Test substance	: 2,6-Dimethyl xylenol, purity >99%
Reliability	: (1) Reliable without restriction.

(22) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 46, 1997.

DEVELOPMENTAL TOXICITY
2,6-Xylenol (CAS 576-26-l)

Type	: Teratology
Species	: Rat
Sex	: 24 pregnant females per group
Strain	: SD
Route of administration	: Oral gavage
Exposure period	: days 6-l 5 of gestation
Frequency of treatment	: daily
Post exposure period	: Sacrifice GD 20
Doses	: 0, 60, 180 and 540 mg/kg/day
Control groups	: vehicle
NOAEL	: 180 mg/kg/day
Results	: Maternal toxicity (body weight gain suppression) at 180 mg/kg/day and higher; maternal mortality (2/24) at the high-dose. Developmental toxicity (reduced fetal weight) at 540 mg/kg/day.
Year	: 1997
GLP	: Yes
Test substance	: 2,6-Dimethyl xylenol, purity >99%
Reliability	: (1) Reliable without restriction.

(23) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 48, 1997.

ECOTOXICITY ELEMENTS
2,6-Xylenol (CAS 576-26-l)

Type	: Acute prolonged
Species	: Fathead minnow
Sex	: Not stated
Strain	: Not applicable
Route of administration	: Flow-through
Exposure period	: 96 hr and 8 days
Frequency of treatment	: Continuous
Post exposure period	: Not applicable
Doses	: Not stated, analytical verification employed
Control group	: Untreated
LC50	: >27 mg/l for 96 hours; 23 mg/l for 192 hours

Method	: Evaluate test water quality, fish behavior and pharmacotoxic signs, body weight and survival.
Year	: 1981
GLP	: Not stated
Test substance	: 2,6-Dimethyl xylenol, purity not stated

Reliability : (2) Reliable with restrictions

(24) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 19, 1997.

Type	: Acute
Species	: Daphnia magna
Sex	: Not aplicable
Strain	: Not applicable
Route of administration	: Static bioassay
Exposure period	: 96hr
Frequency of treatment	: Continuous
Post exposure period	: Not applicable
Doses	: Not stated
Control group	: Untreated
IC50	: 11.2 mg/l
Year	: 1974
GLP	: Not stated
Test substance	: 2,6-Dimethyl xylenol, purity not stated
Reliability	: (2) Reliable with restrictions

(25) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 20, 1997.

Type	: Acute algae
Species	: Tetrahymena pyriformis
Sex	: Not aplicable
Strain	: Not applicable
Route of administration	: Static bioassay
Exposure period	: 24 hr
Frequency of treatment	: Continuous
Post exposure period	: Not applicable
Doses	: Not stated
Control group	: Untreated
LC100	: 325 mg/l; NOEC not calculated
Year	: 1978
GLP	: Not stated
Test substance	: 2,6-Dimethyl xylenol, purity not stated
Reliability	: (3) Not reliable

(26) SIDS Dossier 2,6-Dimethylphenol. Sponsor Country USA, p. 23, 1997.

APPENDIX F
ROBUST SUMMARIES FOR 3,4-XYLENOL STUDIES SUPPORTING THE MIXED XYLENOLS CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
3,4-Xylenol (CAS 95-65-8)

Type	: Melting Point
Value	: 65.1 °C
Decomposition	: No
Sublimation	: No
Method	: unknown
Year	: unknown
GLP	: unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR value taken from Texas A&M Thermodynamics Research Center "Key Chemical Data Books – Xylenols", 1978, plus two other sources.

Type	: Boiling Point
Value	: 227.0 °C
Decomposition	: No
Sublimation	: No
Method	: unknown
Year	: unknown
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR value taken from Texas A&M Thermodynamics Research Center "Key Chemical Data Books – Xylenols", 1978, plus two other sources.

Type	: Vapor Pressure
Value	: 0.04 mmHg at 25°C
Method	: Calculated from vapor pressure constants in reference
GLP	: unknown
Year	: unknown
Remarks	: None
Quality	: Estimated < 3% error
Reliability	: (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR values regressed from three literature references.

Type	: Partition Coefficient
Value	: Log Kow = 2.33
Method	: unknown
GLP	: unknown
Year	unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(4) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Water Solubility
Value	: 4760 mg/L @ 25°C
Method	: uknown
GLP	: unknown
Year	: Unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(5) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: pKa Value
Value	: 10.35
Method	: unknown
GLP	: Unknown
Year	: unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(6) Ulhnann's Encyclopedia of Industrial Chemistry (1985), Vol. A8, p. 48.

ENVIRONMENTAL FATE ELEMENTS
3,4-Xylenol (CAS 95-65-8)

Type	: Atmospheric fate
Value	: T1/2 = 4.7 hours
Method	: Structure activated method
GLP	: Unknown
Year	: 1993
Remarks	: Vapor-phase 3,4-xylenol was' degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles

Reaction rate constant = 8.14x10S-11 cc/molecule-set @ 25°C
Quality : unknown
Reliability : (4) Not Assignable

(7) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : Aerobic soil degradation
Value : Complete after 9 days
Method : Incubation with unacclimated soil @ 19°C
GLP : Unknown
Year : 1981
Remarks : Laboratory study
Quality : unknown
Reliability : (4) Not Assignable

(8) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : Aqueous aerobic degradation
Value : Below detection level in 14 days
Method : Contaminated groundwater water in shake flask
GLP : Unknown
Year : 1991
Remarks : Laboratory study
Quality : Unknown
Reliability : (4) Not Assignable

(9) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

MAMMALIAN TOXICOLOGY ELEMENTS
3,4-Xylenol (CAS 95-65-8)

Type : Acute
Species : Mouse
Sex : Not stated
Strain : Not stated
Route of administration : Oral
Exposure period : NA
Frequency of treatment : One day
Post exposure period : Not stated
Doses : Not stated
Control group : Not stated
LC50 : 400 mg/kg
Method : Not stated
Year : 1996
GLP : No

Test substance	: 3,4-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(10) Lewis, R. J., Sax's Dangerous Properties of Industrial Materials. 9th edition. p 3406, Van Nostrand, New York, 1996.

Type	: Acute
Species	: Rabbit
Sex	: Not stated
Strain	: Not stated
Route of administration	: Oral
Exposure period	:NA
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: Not stated
Control group	: Not stated
LC50	: 800 mg/kg
Method	: Not stated
Year	: 1996
GLP	: No
Test substance	: 3,4-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(11) Lewis, R. J., Sax's Dangerous Properties of Industrial Materials. 9th edition. p 3406, Van Nostrand, New York, 1996.

GENETIC TOXICITY IN VITRO
3,4-Xylenol (CAS 95-65-8)

Type	: Ames test
System of testing	: Salmonella typhimurium TA 98 and TA 100
Test concentration	: Not stated
Metabolic activiation	: Not stated
Result	: Negative for mutagenicity
Year	: 1979
Test substance	: Purity not stated
GLP	: No information
Remark	: Work appears to have been conducted on shale oil products and derivatives
Reliability	: (3) Not Reliable

(12) Epler, J. L., et al. Environ Health Persp., 30: 179-184, 1979.

ECOTOXICITY ELEMENTS
3,4-Xylenol (CAS 95-65-8)

Type	: Acute
Species	: Fathead minnow
Sex	: Not stated
Strain	: Not applicable
Route of administration	: Static bioassay
Exposure period	: 48 hr
Frequency of treatment	: Continuous
Post exposure period	: Not applicable
Doses	: Not stated
Control group	: Untreated
LC50	: 15 mg/l for 48 hours; 14 mg/l for 72 hours and 14 mg/l for 96 hrs
Year	: 1983
GLP	: Not stated
Test substance	: 3,4-Dimethyl xylenol, purity not stated
Reliability	: (2) Reliable with restrictions

(13) Verschueren, K., Handbook of Environmental Data of Organic Chemiclas, 2nd edition. New York, Van Nostrand, p 1197, 1983.

APPENDIX G
ROBUST SUMMARIES FOR 3,5-XYLENOL STUDIES SUPPORTING THE MIXED XYLENOLS CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
3,5-Xylenol (CAS 108-68-9)

Type	: Melting Point
Value	: 63.44 °C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: unknown
GLP	: unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980, plus additional literature references.

Type	: Boiling Point
Value	: 221.74 °C
Decomposition	: No
Sublimation	: No
Method	: unknown
Year	: unknown
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR value taken from Texas A&M Thermodynamics Research Center "Key Chemical Data Books – Xylenols", 1978, plus two other sources.

Type	: Vapor Pressure
Value	: 0.04 mmHg at 25°C
Method	: Calculated from vapor pressure constants in reference
GLP	: unknown
Year	: unknown
Remarks	: None
Quality	: Estimated < 3% error
Reliability	: (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) Revised 1996, DIPPR values regressed from three literature references.

Type	: Partition Coefficient
Value	: Log Kow = 2.35
Method	: Unknown
GLP	: unknown
Year	: unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(4) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Log Kow
Value	: 2.35
Method	: Unknown
GLP	: Unknown
Year	: unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(5) International Labour Organization, International Occupational Safety and Health Information Centre, ICSC : 1356

Type	: Log Kow
Value	: 2.06 / 2.55
Method	: Unknown / Unknown
GLP	: Unknown / Unknown
Year	: Unknown / Unknown
Remarks	: None / None
Quality	: Unknown / Unknown
Reliability	: (2) Reliable with restrictions

(6) Verschueren, "Handbook of Environmental Data on Organic Chemicals"

Type	: Water Solubility
Value	: 4880 mg/L @ 25°C
Method	: Uknown
GLP	: unknown
Year	: unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(7) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: pKa Value
Value	: 10.19 @ 25°C
Method	: Unknown
GLP	: unknown
Year	: unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(8) : Ullmann's Encyclopedia of Industrial Chemistry (1985), Vol. A8, p. 48

ENVIRONMENTAL FATE ELEMENTS
3,5-Xylenol (CAS 108-68-9)

Type	: Atmospheric fate
Value	: T1/2 = 3.4 hours
Method	: Structure activated method
GLP	: Unknown
Year	: 1993
Remarks	: Vapor-phase 3,5-xylenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles Reaction rate constant = 1.13x1 OS-l 1 cc/molecule-set @ 25°C
Quality	: Unknown
Reliability	: (4) Not Assignable

(9) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aerobic soil degradation
Value	: Complete after 1 ldays
Method	: Incubation with unacclimated soil @ 19°C
GLP	: Unknown
Year	: 1981
Remarks	: Laboratory study
Quality	: unknown
Reliability	: (4) Not Assignable

(10) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aqueous aerobic degradation
Value	: Below detection level in 14 days
Method	: Contaminated groundwater water in shake flask
GLP	: Unknown
Year	: 1991

Remarks	: Laboratory study
Quality	: unknown
Reliability	: (4) Not Assignable

(11) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

MAMMALIAN TOXICOLOGY ELEMENTS
3,5-Xylenol (CAS 108-68-g)

Type	: Acute
Species	: Rat
Sex	: Not stated
Strain	: Not stated
Route of administration	: Oral
Exposure period	: NA
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: Not stated
Control group	: Not stated
LC50	: 608 mg/kg
Method	: Not stated
Year	: 1996
GLP	: No
Test substance	: 3,5-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(12) Lewis, R. J., Sax's Dangerous Properties of Industrial Materials. 9th edition. p 3406, Van Nostrand, New York, 1996.

Type	: Acute
Species	: Rabbit
Sex	: Not stated
Strain	: Not stated
Route of administration	: Oral
Exposure period	: NA
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: Not stated
Control group	: Not stated
LC50	: 1313 mg/kg
Method	: Not stated
Year	: 1996
GLP	: No
Test substance	: 3,5-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(13) Lewis, R. J., Sax's Dangerous Properties of Industrial Materials. 9th edition. p 3406, Van Nostrand, New York, 1996.

Type	: Acute
Species	: Mouse
Sex	: Not stated
Strain	: Not stated
Route of administration	: Oral
Exposure period	:NA
Frequency of treatment	: One day
Post exposure period	: Not stated
Doses	: Not stated
Control group	: Not stated
LC50	: 477 mg/kg
Method	: Not stated
Year	: 1996
GLP	: No
Test substance	: 3,5-Dimethyl xylenol, purity not stated
Reliability	: (4) Not assignable

(14) Lewis, R. J., Sax's Dangerous Properties of Industrial Materials. 9th edition. p 3406, Van Nostrand, New York, 1996.

ECOTOXICITY ELEMENTS
3,4-Xylenol (CAS 95-65-8)

Type	: Acute
Species	: Carp
Sex	: Not stated
Strain	: Not applicable
Route of administration	: Not stated
Exposure period	: 24 hr
Frequency of treatment	: Continuous
Post exposure period	: Not applicable
Doses	: Not stated
Control group	: Not stated
TMlo	: 53 mg/l
Year	: 1983
GLP	: Not stated
Test substance	: 3,4-Dimethyl xylenol, purity not stated
Reliability	: (3) Not reliable

(15) Verschueren, K., Handbook of Environmental Data of Organic Chemiclas, 2nd edition. New York, Van Nostrand, p 1197, 1983.

Type	: Acute
Species	: Fathead minnow
Sex	: Not stated
Strain	: Not applicable
Route of administration	: Static bioassay
Exposure period	: 48 hr
Frequency of treatment	: Continuous
Post exposure period	: Not applicable
Doses	: Not stated
Control group	: Untreated
LC50	: 15 mg/l for 48 hours; 14 mg/l for 72 hours and 14 mg/l for 96 hrs
Year	: 1983
GLP	: Not stated
Test substance	: 3,4-Dimethyl xylenol, purity not stated
Reliability	: (2) Reliable with restrictions

(16) Verschueren, K., Handbook of Environmental Data of Organic Chemiclas, 2nd edition. New York, Van Nostrand, p 1198, 1983.

APPENDIX H
ROBUST SUMMARIES FOR m-CRESOL TOXICITY STUDIES SUPPORTING THE MIXED XYLENOLS CATEGORY

REPEATED-DOSE TOXICITY

Type	Repeated dose
Species	Rat
Sex	Male
Strain	no data
Route of admin.	oral feed
Exposure period	28 d
Frequency of treatm.	Daily
Post exposure period	No
Doses	0, 20, 150, 500 mg/kg diet (approx. 0, 1.86, 13.95 or 45.8 mg/kg bw/d)
Control group	yes, concurrent no treatment
NOAEL	ca. 45.8 ty mglkg bw
Method	other: 10 rats/group, TS was prepared as a 2.0% corn oil solution and blended with the diet; diets were prepared fresh weekly. Control rats received basal diets containing 2% corn oil, necropsy of all animals
Year	1969
GLP	no data
Test substance	other TS: M.P.:Il-12 C; B.P.: 202.8 C
Result	No deaths occurred during the study and no untoward behavioural reactions were noted. At necropsy, no significant gross lesions were noted among the test animals, when compared to the control animals.

(1)

Type	Repeated dose
Species	Rat
Sex	male/female
Strain	other: F344/N
Route of admin.	oral feed
Exposure period	28 days
Frequency of treatm.	continuously in diet
Post exposure period	No
Doses	0,300, 1000, 3000, 10000 or 30000 ppm (see remarks)
Control group	Yes
NOAEL	10000 ppm
Method	other: 5 rats/sex and dose, clinical observations twice daily, body weight initially, weekly and at termination, gross and microscopic examination, statistical analysis
Year	1991
GLP	Yes
Test substance	other TS: purity > 98%
Remark	mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	**25**	**25**

	1000 ppm	85 82
	3000 ppm	252 252
	10000 ppm	870 862
	30000 ppm	2470 2310
Result	:	no mortallity; no clinical signs of toxicity were observed and no gross lesions were noted at necropsy
		>= 10000 ppm: increased relative liver weights for males and females, but no histomorphologic changes 30000 ppm: decreased mean final body weights and mean body weight gains for males and females; reduced food consumption in males and females during the first week of the study; relative kidney weight marginally increased in males and females but no histomorphologic changes; minimal to mild uterine atrophy in 4 of 5 females
		NOAEL: male: 870 mg/kg bw NOAEL: female: 862 mg/kg bw
Reliability		(1) valid without restriction

(2)

Type	.	Repeated dose
Species		Rat
Sex	.	male/female
Strain	.	Sprague-Dawley
Route of admin.	.	Gavage
Exposure period	.	13 w
Frequency of treatm.	.	once daily
Post exposure period	:	l w
Doses		0, 50, 150 or 450 mg/kg bw/d in corn oil
Control group	.	yes, concurrent vehicle
Method	.	other: 30 rats/sex/dose, add.10 rats/sex for baseline clin. Pathol., interim kill at week 7, terminal kill at week 14, blood samples for hematology, clin.chemistry; urinalysis; gross and microsc. pathology; stat. anal.: Dunnett's t-t
Year	:	1988
GLP		Yes
Test substance	.	other TS: purity: 98.6%
Result	.	signs of intoxication: 450 mg/kg bw, male, female: lethargy, tremors, hunched posture, dyspnea; >= 150 mg/kg bw: slight reduction in body weight gain of males 450 mg/kg: one high dose male was found dead on day 5 (cause not evident), reductions in weight gain for males and females; treatment-related gross and histomorphologic lesions not evident
		NOAEL: 50 mg/kg bw (male) NOAEL: 150 mg/kg (female)
Reliability		(2) valid with restrictions

(3)

Type		Repeated dose
Species	:	Rat

Sex	:	male/female
Strain	:	other: CD
Route of admin.	:	Gavage
Exposure period		13 w
Frequency of treatm.		Daily
Post exposure period	:	no data
Doses	:	50, 150 or 450 mg/kg bw/d in corn oil
Control group	:	yes, concurrent vehicle
LOAEL	:	ca. 50 mg/kg bw
Method	.	other: 10 rats/sex and group, observation of clinical signs, performance of neuro-behavioural test batteries, gross pathologic and histopathologic evaluation
Year	.	1986
GLP		no data
Test substance	.	other TS: no data on purity
Result	.	>= 50 mg/kg: salivation, hypoactivity, rapid laboured breathing 450 mg/kg: one female was found dead; increased closing of eyelids, pollakisuria (females), reduced food consumption; few significant changes in the performance of the neuro-behavioural test batteries (no further details reported); no brain weight changes, no gross or histopathological lesions in the brain or other nervous tissue

(4)

Type	.	Repeated dose
Species	.	Mouse
Sex		male/female
Strain		B6C3F1
Route of admin.	.	oral feed
Exposure period	.	28 days
Frequency of treatm.	.	continuously in diet
Post exposure period	.	No
Doses		0, 300, 1000, 3000, 10000 or 30000 ppm (see remarks)
Control group	.	Yes
NOAEL		ca. 3000 ppm
Method	.	other: 5 mice/sex and dose, clinical observations twice daily, body weight initially, weekly and at termination, organ weights recorded and microscopically examined, statistical analysis
Year		1991
GLP	.	Yes
Test substance	.	other TS: purity > 98%
Remark	:	mean compound consumption (mg/kg bw/day): males females 0 ppm 0 0 300 ppm 53 66 1000 ppm 193 210 3000 ppm 521 651 10000 ppm 1730 2080 30000 ppm 4710 4940
Result		mortality: 0 ppm: 1/5 male; 10000 ppm: 1/5 females; 300000 ppm: 2/5

males, 2/5 females;
Signs of toxicty: male, female; >= 100000 ppm:
hunched posture, rough hair coat, laboured respiration (only females), additionally at 30000 ppm: thin appearance, lethargy and tremor
relative liver weight increased: male from 3000 ppm, female from 300 ppm
relative kidney weight increased: male at 3000 ppm, female at 30000 ppm
histomorphology: female: 30000 ppm: mammary gland, ovarian and uterine atrophy

NOAEL (male): 521 mg/kg bw
NOAEL (female): 651 mg/kg bw

Reliability : (1) valid without restriction

(2)

Type : Repeated dose
Species : Mouse
Sex : Female
Strain : other: CBA/J
Route of admin. : Dermal
Exposure period : 6 w
Frequency of treatm. : 3 times/week
Post exposure period : 6 months
Doses : 0.5 % in acetone
Control group : Yes
Method : other: 5 rats, application of the substance to depilated or clipped lower back by mist spray; observation of the hair colour of the new hair regrowth were made weekly
Year : 1974
GLP : no data
Test substance : other TS: no data on purity

Result : No depigmentations of the regrowthed hair were observed.

(5)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Sister chromatid exchange assay
System of testing : human lymphocytes
Test concentration : 0 -1.0 mM

Metabolic activation : no data
Result : Negative
Method : other: solvent: DMSO:EtOH (1:1), culture time 88-90 h
Year : 1986
GLP : no data
Test substance : other TS: purity: 99.2%

(6)

Type : Ames test
System of testing : Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration : over a wide dose range (no further information) in DMSO

Metabolic activation : with and without
Result : Negative
Method : other: according to Ames, Proc.Natl.Acad.Sci.70, 2281(1973); Mutat.Res.31,347(1975); Nestmann, Cancer Res.39.4412(1979); Environ.Mutagen.1,361(1979)
Year : 1980
GLP : no data
Test substance : other TS: purity no data

Remark : presumbly negative, but solubility did not allow the testing of the compound in amounts that result in bacterial toxicity

(7)

Type : Ames test
System of testing : Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537
Test concentration : no data

Metabolic activation : with and without
Result : Negative
Method : other: according to Ames, Mutation Res. 31, 347 (1975)
Year : 1980
GLP : no data
Test substance : other TS: no data on purity

(8)

Type : Unscheduled DNA synthesis
System of testing : rat hepatocytes
Test concentration : 502, 251, 100, 50.2, 25.1, 10.0, 5.02, 2.51, 1.0, 0.502 ug/ml in DMSO

Metabolic activation : With
Result : Negative
Method : other: according to Williams, Cancer Res. 37, 1845 (1977); Williams cited in deSerres (eds): Chemical Mutagens, Vol 8, pp.61, 1980, Plenum Press, NY
Year : 1988
GLP : Yes
Test substance : other TS: 99.8%

Remark : concentration range: 502 - 25.1 ug/ml: excessive toxicity
Reliability : (2) valid with restrictions

(9)

Type : Sister chromatid exchange assay
System of testing : human fibroblasts
Test concentration : 0, 0.08, 0.8, 4 mM dissolved in ethanol; 8, 10, 30 mM dissolved in Eagle's Minimal Essential Medium (MEM)

Metabolic activation : Without
Result : Negative
Method : other: after add. of m-cresol incub. for 2h, then washing and add. of medium containing 15% fetal calf serum and BrdU for 48 h
Year : 1984
GLP : no data
Test substance : other TS: purity: 99%

Remark : > 8 mM cytotoxic response
Reliability : (2) valid with restrictions

(10)

Type : other: DNA amplification
System of testing : SV40-transformed CHO cell
Test concentration : 5.0 mM in DMSO

Metabolic activation : Without
Result : Negative
Method : other: cells were incub. for 4d with m-cresol, then viability of the cells was determined, SV40-DNA content was detected by hybridization according to Lavi, Proc.Natl.Acad.Sci. (USA) 80,6144,1981; Winocour, Proc.Natl.Acad. Sci. (USA) 77,48
Year : 1989
GLP : no data
Test substance : other TS: purity: 98%

(11)

Type : other: SV40 Mammilian Inductest
System of testing : Syrian hamster kidney cells (SV40)
Test concentration : 0.0001-0.0000001 ml

Metabolic activation : Without
Result : Positive
Method : Other
Year : 1983
GLP : No
Test substance : no data

Remark : Mammalian inductest

(12)

Type : Ames test
System of testing : Salmonella typhimurium TA 100, TA 1530, TA 1535, TA 1538,TA 1950, TA 1951, TA 1952, G 46
Test concentration : 0.5% in ethanol

Metabolic activation : no data
Result : Ambiguous
Method : other: according to Ames Mutat. Res. 31,347 (1975); Science 176, 47 (1972)
Year : 1975
GLP : no data
Test substance : other TS: no data on purity

Remark : a questionable effect was produced in the strain TA 1535

(13)

Type : other: SOS-Chromotest
System of testing : Escherichia coli PQ37
Test concentration : no data

Metabolic activation : Without
Result : Positive
Method : other: After termination of the nitrosation of m-cresol with ammonium sulphamate, test was performed according to Quillardet, **Mutat.** Res. **147,65** (1985)
Year : **1989**
GLP : no data
Test substance : other TS: no data

(14)

Type : other: Prophage induction assay
System of testing : Escherichia **coli** / Bacteriophage lambda

Result : Positive

Remark : abstract only

(15)

Type : Cytogenetic assay
System of testing : **Allium** cepa

Metabolic activation : Without
Result : Negative

Year : 1948
GLP : **No**
Test substance : other TS: no data on purity

Remark : marginal effects

(16)

Type : Mouse lymphoma assay
System of testing : L 5178 Y (TK **+/-**) cells
Test concentration : 13.0 - 520 **ug/ml** in DMSO

Metabolic activation : with and without
Result : negative
Method : other: preliminary cytotoxicity tests, procedure according to Clive, Mutation Res. 31 **,17,1975;** Clive, Mutation Res. **59,61 ,1979,** colony size not reported
Year : **1988**
GLP : **yes**
Test substance : other TS: 99.8%

Reliability : (2) valid with restrictions

(17)

Type : Cytogenetic assay

System of testing : Allium cepa
Test concentration : 0, 0.015, 0.02 and 0.025% in destilled water

Metabolic activation : no data
Result : positive
Method : other: treatment period: 0: 3 hrs; 0.015 24 hrs; 0.02: 5 hrs; 0.025: 5 hrs
Year : 1965
GLP : no
Test substance : other TS: no data on purity

(18)

Type : Ames test
System of testing : Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration : 0, 0.5, 5, 50,500, 5000 ug/plate dissolved in DMSO, highest dose toxic

Metabolic activation : with and without
Result : negative
Method : other: plate incorporation assay according to Ames, Mutation Res. 31,347 (1975)
Year : 1982
GLP : no data
Test substance : other TS: purity: 98%

Reliability : (1) valid without restriction

(19)

Type : Ames test
System of testing : Salmonella typhimurium TA98, TA 100, TA 1535, TA 1537
Test concentration : 0.0, 3.3, 10.0, 33.0, 100.0, 333.0 ug/plate in water as solvent

Metabolic activation : with and without
Result : negative
Method : other: preincubation methodology according to Ames, Mutat. Res. 31,347 (1975) and Yahagi, Cancer Lett. 1,91 (1975)<; to select dose range the chemical was checked for toxicity to S. typh. TA 100
Year : 1983
GLP : no data
Test substance : other TS: 97%

Reliability : (1) valid without restriction

(20)

Type : Cytogenetic assay
System of testing : Chinese Hamster Ovary (CHO) cells
Test concentration : 0, 198,297,398,495 ug/ml DMSO without; 0,250, 500,699, 749,799, 898, 998, 999, 1100 ug/ml DMSO with ug/ml: toxic)

Metabolic activation : with and without
Result : negative
Method : other: preliminary range finding studies; in accordance with OECD Guideline 473
Year : 1988

GLP	: **yes**
Test substance	: other TS: purity: 99.8%
Reliability	: (1) valid without restriction

(21)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	: Cytogenetic assay
Species	: other: mouse bone marrow ceils
Sex	: male/female
Strain	: ICR
Route of admin.	: gavage
Exposure period	: once
Doses	0, 96, 320, 960 mg/kg bw in corn oil
Result	: negative
Method	: other: in accordance with OECD Guideline 475, 5 mice/sex/dose, bone marrow ceils, sacrifice 6, 24, 48 hrs post treatment
Year	1989
GLP	yes
Test substance	: other TS: 99.8%
Remark	: dose finding study: see chapter 5.1
Reliability	: (1) valid without restriction

(22)

Type	: Sister chromatid exchange assay
Species	: mouse
Sex	: male
Strain	: DBA
Route of admin.	: i.p.
Exposure period	: single application
Doses	0, 200 mg/kg bw dissolved in sunflower oil
Result	: negative
M e t h o d	: other: 3/4 mice were partly hepatectomized 5 d prior to exposure, 0.5h later BrdU tablets were implanted s.c.; 17h later single i.p. inj. of colchicine, 4h later sacrifice: bone marrow cells, alv. macrophages, regen. liver ceils
Year	: 1984
GLP	: no data
Test substance	: other TS: purity. 99%
Result	: No increase in SCE frequencies in the intact mice as well as in the partially hepatectomized mice.

5.6.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	: rat
Sex	: female
Strain	: Sprague-Dawley
Route of admin.	: gavage
Exposure period	: day 6 through day 15 of gestation

Frequency of treatm. : daily
Duration of test : until gd 21
Doses : 0, 30, 175 or 450 mg/kg bw/d
Control group : yes, concurrent vehicle
NOAEL maternal tox. : ca. 175 mg/kg bw
NOAEL teratogen. : ca.450 mg/kg bw
Method : other: following the TSCA Health Effects Test guidelines for Specific Organ/Tissue Toxicity - Developmental Toxicity (EPA, 1984,1987)
Year : 1988
GLP : yes
Test substance : other TS: purity: 99.4%

Result

450 mg/kg: significant maternal toxicity (reduced food intake, reduced maternal body weights and weight gain during dosing period; reduced gestational weight gain (day O-21); clinical signs of toxicity: hypoactivity, ataxia, tremors, audible respiration, perioral wetness; increased relative liver weights)
no embryotoxicity or teratogenicity was observed at any dosage level

Reliability • (1) valid without restriction

(23)

Species : rabbit
Sex : female
Strain : New Zealand white
Route of admin. : gavage
Exposure period : day 6 through day 18 of gestation
Frequency of treatm. : once daily
Duration of test : until day 29 of gestation
Doses : 0, 50, 150,300 or 500 mg/kg bw/d
Control group : yes

Remark : 8 rabbits/dose
range-finding study

Result : 50 mg/kg: one doe aborted; ataxia, twitching, gasping, audible, labored and rapid respiration; increased relative liver weights
150 mg/kg: maternal mortality 2/8; reduced food consumption on gd 7-9; significantly depressed body weight gain for gd 6-12; cleft palace in 1 fetus
>= 300 mg/kg: reduced food consumption on gd 6-10; significantly elevated clinicals signs of toxicity (CNS and cardiopulmonary categories; see at 50 mg/kg)
300 mg/kg: maternal mortality 118; one doe aborted: reduced body weight on gd 12 and significantly depressed body weight gain on gd 6-12; increased preimplantation loss and increase in dead fetuses/litter; forelimb and pectoral girdle anomalies in 4 fetuses in 2 litters; cleft palate in 1 fetus; small tongue

500 mg/kg: maternal mortality 8/8

(24)

Species	:	rabbit
Sex	:	female
Strain	:	New Zealand white
Route of admin.	:	gavage
Exposure period	:	day 6 through day 18 of gestation
Frequency of treatm.		once daily
Duration of test	:	until day 29 of gestation
Doses	:	0,550 or 100 mg/kg bw/day
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.		ca. 5 mg/kg bw
NOAEL teratogen.		ca. 100 mg/kg bw
Method		other: following the TSCA Health Effects Test guidelines for Specific Organ/Tissue Toxicity - Developmental Toxicity (EPA, 1984,1987)
Year		1988
GLP		yes
Test substance		other TS: purity: 99.7%

Result	:	>= 50 mg/kg: audible respiration and ocular discharge No embryotoxicity or teratogenicity was observed at any dosage employed.
Reliability	:	(1) valid without restriction

(25)

Species	:	rat
Sex	:	female
Strain	:	Wistar
Route of admin.	:	s.c.
Exposure period	:	day 7 through day 17 of gestation
Frequency of treatm.	:	daily
Duration of test	:	until post partum
Doses	:	90 mg/kg bw/d (30 ml/kg bw 0.3%)
Control group	:	yes

Result	:	m-cresol was used as the solvent at a concentration of 0.3 %; no negative effects on FO- or Fl-generation were observed when compared with control animals.

(26)

Species	:	rat
Sex	:	female
Strain	:	Wistar
Route of admin.		s.c.
Exposure period	:	day 17 of gestation until 21 days after birth
Frequency of treatm.	:	daily
Duration of test		until 8 w post pat-turn
Doses	:	90 mg/kg bw/d (30 mg/kg 0.3%)
Control group	:	yes

Result	:	m-cresol was used as the solvent at a concentration of 0.3%; no negative effects on FO-, F1- or F2-generation were observed when compared with controls (no fetotoxicity,

normal postnatal development, normal behaviour and fertility).

(27)

Species	: mouse
Sex	: female
Strain	: other: ICR-SLC
Route of admin.	: **S.C.**
Exposure period	: day 6 through day 15 of gestation
Frequency of treatm.	: daily
Duration of test	: until 5 w post partum
Doses	: no data
Control group	: yes
Result	: m-cresol was used as the solvent; no signs of fetotoxicity or teratogenicity, no maternal toxicity.

(28)

Species	: rabbit
Sex	: female
Strain	: no data
Route of admin.	: **s.c.**
Exposure period	: day 6 through day 18 of gestation
Frequency of treatm.	: daily
Duration of test	: until >= 12 d after exposure
Doses	: 30 mg/kg bw/d (10 ml/kg 0.3%)
Control group	: Yes
Result	: m-cresol was used as the solvent at a concentration of 0.3%; decreased maternal food consumption and body weight gain after day 14 of gestation, increased average number of implantations and reduced mean body weights in male fetuses, no increase of anomalies.

(29)

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APPENDIX I
ROBUST SUMMARIES FOR p-CRESOL TOXICITY STUDIES SUPPORTING THE MIXED XYLENOLS CATEGORY

REPEATED-DOSE TOXICITY

Type		Repeat dose
Species		Rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period		28 days
Frequency of treatm.	:	ad libitum
Post exposure period	:	None
Doses		0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	83 - 87 mg/kg bw
LOAEL	:	242 - 256 mg/kg bw
Method		EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance	:	other TS: purity > 98%

Remark : Groups of five rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination.

mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	25	25
1000 ppm	87	83
3000 ppm	256	242
10000 ppm	835	769
30000 ppm	2180	2060

At necropsy, the brain, heart, tight kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.

Result There were no deaths. Decreased mean final body weights, body weight gains and feed consumption occurred in both the top-dose males and females. These animals also showed clinical signs of toxicity, including hunched posture and rough hair coat.
Increased relative liver and kidney weights were recorded in

females fed >/= 242 mg/kg bw/day or 2060
respectively and in males fed >/= 835 No
gross lesions were noted at necropsy.
Histopathological evaluation revealed effects in the uterus in the top-dose females; in the nasal cavity in both males and females at >/= 256 and >/= 242 mg/kg bw/day, respectively; and bone marrow in both males and females at >/= 256 and >/= 769 mglkg bwlday, respectively.

Reliability : (1) valid without restriction

(1)

Type	: Repeat dose
Species	: Mouse
Sex	: male/female
Strain	: B6C3F1
Route of admin.	oral feed
Exposure period	: 28 days
Frequency of treatm.	: ad libitum
Post exposure period	: None
Doses	: 0, 300, 1000, 3000, 10000, 30000 ppm
Control group	: yes, concurrent no treatment
NOAEL	: 50 - 60 mg/kg bw
LOAEL	60 - 163 mg/kg bw
Method	: EPA OTS 795.2600
Year	: 1992
GLP	: Yes
Test substance	: other TS: purity > 98%

Remark : Groups of five mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination.

mean compound consumption (mg/kg bwlday):

	males	females
0 ppm	0	0
300 ppm	50	60
1000 ppm	163	207
3000 ppm	469	564
10000 ppm	1410	1590

Consumption data for the top dose were not calculated due to 100% mortality at this level.

At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.

Result : There was 100% mortality at the highest dose level. One male receiving 1410 also died. Mean final body weights and mean body weight gains for surviving males at 1410 were significantly lower than in the control groups; feed consumption was

depressed at the beginning of the study in males at 1410 mg/kg bw/day and in females at 1590
Clinical signs of toxicity included hunched posture, rough hair coat, lethargy, and hypothermia in the top-dose females that died and, together with laboured breathing and paleness, in the males fed >/= 1410
Relative liver weight was increased in females receiving >/= 564 mg/kg bw/day; in males, the relative liver and heart weights were increased at 1410 mg/kg bw/day and relative kidney weight at >/= 469 mg/kg bw/day. No gross lesions were noted at necropsy.
Histopathological evaluation revealed nasal lesions in the females at all doses and in males at >/= 163 mg/kg bw/day. In the top-dose animals which died, renal and hepatic necrosis and bone marrow hypocellularity was noted.

Reliability : (1) valid without restriction

(1)

Type : Repeat dose
Species : Rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : Gavage
Exposure period : 13 weeks
Frequency of treatm. : 7 days/week

Doses : 0, 50, 175,600 mg/kg bw/day
Control group : Yes
LOAEL : 50 mg/kg bw
Method : other
Year :
GLP : no data
Test substance : no data

Remark Groups of 30 rats/sex were administered p-cresol in corn oil. The original data are unpublished and are available from the US EPA Freedom of Information Office. No further experimental details are available from the citing reviews (ATSDR, 1990; IPCS, 1993).

Result 600 mg/kg: There was some mortality. Overt signs of toxicity at this dose included lethargy, tremors, convulsions and coma. There was also a decrease in the body weight gains. In females, increased serum enzyme levels were observed, which were correlated with the presence of hepatic inflammation, and serum cholesterol. The relative heart and liver weights of males were increased and their absolute brain weight decreased. Females showed decreased absolute brain and ovary weights. Microscopic examination revealed a small increased incidence of epithelial metaplasia of the trachea in both sexes.
>/= 175 mg/kg: serum protein levels and relative kidney weight were increased in the males and blood effects (decreased red blood cell count and haemoglobin and haematocrit values) observed in the females.
A small increase in the incidence of nephropathy, which did

not appear to be dose-related, was seen in the males at all dose levels.

Reliability : (2) valid with restrictions

(2)

GENETIC TOXICITY 'IN VITRO'

Type . Ames test
System of testing . Salmonella typhimurium TA 98, 100, 1535, 1537.
Test concentration . 0.0, 3.3, 10.0, 33.0, 100.0, 333.0 ug/plate in water as solvent

Metabolic activation . with and without
Result . Negative
Method . other: preincubation methodology according to Ames, Mutat. Res. 31, 347 (1975) and Yahagi, Cancer Lett. 1, 91 (1975; to select dose range the chemical was checked for toxicity to S. typh. TA100
Year : 1983
GLP no data
Test substance . other TS: purity >97%

Remark This endpoint had been studied by other investigators and results are similar to the study mentioned above.
Reliability . (1) valid without restriction

(3)

Type : Cytogenetic assay
System of testing : Chinese hamster ovary cells
Test concentration 30 to 902 ug/ml

Metabolic activation . with and without
Result Positive
Method : other: similar to OECD Guideline 473

GLP Yes
Test substance : other TS: 99.8% pure

Method . Duplicate CHO cultures were incubated with 15-301 ug/ml of the test substance in the nonactivation aberrations assay. The metabolic activation cultures were treated with 30-300 ug/ml of the test substance in a 10 hour assay and with 301-902 ug/ml in a 20 hour assay.
Result . Increases in chromosomally aberrant cells were observed in the nonactivation assay at all doses. Increases in the chromosomally aberrant cells were observed in the 20 hour assay with metabolic activation at 301 and 601 ug/ml.
Reliability : (1) valid without restriction

(4)

Type : other: cell transformation assay
System of testing : mouse BALB/c-3T3 cells
Test concentration : 0.81 nl/ml, 3.25 nllml, 5 nllml, 1'0 nllml, and 15 nllml

Cycotoxic concentr.	: 31.3 nl/ml
Metabolic activation	: Without
Result	: Positive
Method	: EPA OTS 795.2850
Year	: **1988**
GLP	: **Yes**
Test substance	: other TS: 99.8% pure

Reliability : (1) valid without restriction

(5)

Type	: Mouse lymphoma assay
System of testing	: L5178Y mouse lymphoma cells
Test concentration	: with activation: 0.256 ug/ml, 0.511 ug/ml, 0.767 ug/ml, 1.02 ug/ml, 1.53 ug/ml, and 3.07 ug/ml. without activation: 51.1 ug/ml, 102 ug/ml, 153 ug/ml, 204 ug/ml, 307 ug/l, and 409 ug/ml.
Cycotoxic concentr.	: with activation: 5.11 ug/ml. without activation: 511 ug/ml.
Metabolic activation	: with and without
Result	: Negative
Method	: other: similar to OECD Guideline 476
Year	: 1988
GLP	: Yes
Test substance	: other TS: 99.8% pure

Reliability : (1) valid without restriction

(6)

Type	: DNA damage and repair assay
System of testing	: human lymphocytes
Test concentration	: 5 x 10-6 - 25 x 10-6 M
Metabolic activation	: Without
Result	: Positive
Method	: Other
Year	: 1986
GLP	: no data
Test substance	: other TS: p-cresol, purity not noted

Method : pCresol was tested for its ability to inhibit semiconservative DNA synthesis. Initially, DNA repair was induced by irradiation and, in these cells, semiconservative DNA synthesis was blocked by treatment with with hydroxyurea. In both studies, cells were treated with radiolabelled thymidine for 2 hours and incorporation of thymidine into the cells was measured.

Result : p-Cresol inhibited both UV-induced DNA repair synthesis and semiconservative DNA synthesis as seen by a reduction in radiolabelled thymidine incorporation. tt was unclear from the report if this inhibition was seen at all concentrations tested but at the top dose, 21% inhibition of DNA repair synthesis and 25% inhibition of semiconservative DNA synthesis was found.

(7)

Type	:	Sister chromatid exchange assay
System of testing		human lymohocytes
Test concentration		0 - OS Mm
Metabolic activation	:	no data
Result	:	Negative
Method		Other
Year	:	1986
GLP		no data
Test substance	:	other TS: p-cresol, 99.9% purity
Remark		Styrene-7,8-oxide acted as the positive control. Cells were incubated with p-cresol for 88-90 hr before being analysed. This endpoint had been studied by another investigator and reported results similar to the study mentioned above.

(8) (9)

Type		Ames test
System of testing	:	Salmonella typhimurium strains TA98, 100, 1535, 1537, TA1538
Test concentration	:	0, 0.5, 5, 50, 500, 5000 ug/plate dissolved in DMSO, highest dose cytotoxic
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: preincubation methodology according to Ames, Mutation Res. 31, 347 (1975)
Year	:	1975
GLP	:	no data
Test substance		other TS: purity : 98%
Reliability	:	(1) valid without restriction

(10)

GENETIC TOXICITY 'IN VIVO'

Type	:	Dominant lethal assay
Species	:	Mouse
Sex	:	male/female
Strain	:	ICR
Route of admin.	:	Gavage
Exposure period	:	Single dose
Doses	:	0, 100, 275, and 550 mg/kg
Result	:	Negative
Method	:	EPA OTS 798.5450
Year	:	1989
GLP	:	Yes
Test substance	:	other TS: 99.8% pure
Reliability	:	(1) valid without restriction

(11)

Type	: Drosophila SLRL test
Species	: Drosophila melanogaster
Sex	: Male
Strain	: other: Oregon-R
Route of admin.	: oral feed
Exposure period	: 3 days
Doses	: 0, 60, 300 and 600 ug/ml 5% sucrose
Result	: Negative
Method	: EPA OTS 798.5275
Year	: 1989
GLP	: Yes
Test substance	: other TS: 99.8% purity

Reliability : (1) valid without restriction

(12)

Type	: Sister chromatid exchange assay
Species	: Mouse
Sex	: Male
Strain	: DBA
Route of admin.	: i.p.
Exposure period	: single dose
Doses	: 0, 75 mg/kg bw in sunflower oil
Result	: Negative
Method	: other
Year	: 1984
GLP	: no data
Test substance	: other TS: p-cresol, purity >99%; obtained from Aldrich Chemical Co.

Method : p-Cresol was administered to 2 or 3 intact or hepatectomized male mice by single intraperitoneal injection. Negative and positive controls received 0.35 ml sunflower oil (4 intact and 5 hepatectomized animals) and 5 mg cyclophosphamide/kg bw (2 intact animals), respectively. After 30 min, DNA labelling was initiated using BrdU. After a further 21 hr the animals were killed, cells isolated and harvested and sister chromatid exchange (SCE) frequency in bone marrow cells, alveolar macrophages and regenerating liver cells analysed. Some of the mice were partially hepatectomized to induce liver cell regeneration.

Result : p-Cresol did not induce significant increases in SCE frequencies in any of the cell types examined. The doses tested were overtty toxic to the mice, causing lethargy, piloerection and lacrimation.

Reliability : (2) valid with restrictions

(13)

TOXICITY TO FERTILITY

Type	:	Two generation study
Species	:	Rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	see remarks
Frequency of treatm.	:	5 days per week
Premating exposure period		
Male	:	10 weeks
Female	:	10 weeks
Duration of test	:	see remarks
No. of generation studies	:	2
Doses		0, 30, 175, 450 mg/kg bw/day; 25 rats/sex/group
Control group	:	yes, concurrent vehicle
NOAEL parental	:	ca. 30 mg/kg bw
NOAEL F1 offspring	:	ca. 175 mg/kg bw
NOAEL F2 offspring	:	ca. 175 mg/kg bw
other: NOAEL (fertility)	:	ca. 450 mg/kg bw
Method		EPA OPP 83-4
Year	:	1989
GLP		Yes
Test substance	:	other TS: 98.93% pure

Remark : Groups of rats were administered p-cresol in corn oil. Exposure began 10 weeks prior to breeding and continued in the females throughout mating, gestation and lactation. The offspring were gavaged with the same doses as their respective parents for 11 weeks; the females again being dosed throughout mating, gestation and lactation. The F2 offspring were sacrificed at weaning.

Result : Clinical signs of toxicity occurred in FO and F1 males and females at 450 mg/kg bw/day and included hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration, perinasal encrustation (not in FO males), and perioral wetness occurred at >= 175 mg/kg bw.

No reproductive parameters were effected in either of the two generations (F1 or F2).
p-Cresol caused increased still births in the F1 and F2 generations: in F1 pups at 175 (but not 450) mg/kg/day and in F2 pups at 30 and 450 (but not 175) mg/kg/day. There was some variability in the number of stillborn in control groups in F1 and F2 generation (2 versus 0) and there was no clear dose-dependent effect in both generations (control/low/mid/high dose: F1 pups: 2/4/13/6; F2 pups: O/7/4/9). In F2 (but not F1) live birth indices were reduced at 30 and 450 (not 175) mg/kg/day. Without any other effects especially in the 30 mg/kg bw-group it is unclear whether the effects on live birth indices were substance related. Pup survival indices in both generations were not affected by treatment.

Reliability (1) valid without restriction

(14)

DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	Rat
Sex	Female
Strain	Sprague-Dawiey
Route of admin.	Gavage
Exposure period	days 6 – 15
Frequency of treatm.	Daily
Duration of test	10 days
Doses	0, 30, 175, 450 mg/kg bw/day; 25 inseminated females/group
Control group	yes, concurrent vehicle
NOAEL maternal tox.	= 175 mg/kg bw
NOAEL teratogen.	= 175 mg/kg bw
Method	EPA OPP 83-3
Year	1988
GLP	Yes
Test substance	Other TS: p-cresoi. purity = 98.93%
Remark	p-Cresoi was administered in corn oil.
Result	Maternal toxicity occurred at 450 mg/kg bw/day and included death, decreased food consumption and body weight gain, audible respiration, hypoactivity, ataxia and tremors. p-Cresol caused mild fetotoxicity at the 450 mg/kg, as seen by reduced ossification in three skeletal districts. in addition, fetal body weight was reduced at the 450 mg/kg dose level. There was no treatment-related increased incidence of malformations at any dosage.
Reliability	(1) valid without restriction

(15)

Species	Rabbit
Sex	Female
Strain	New Zealand white
Route of admin.	Gavage
Exposure period	Days 6 - 18 of gestation
Frequency of treatm.	Daily
Duration of test	24 days
Doses	0, 5, 50, 100 mg/kg bw/day; 14 inseminated females/group
Control group	yes, concurrent vehicle
NOAEL maternal tox.	< 50 mg/kg bw
NOAEL teratogen.	= 100 mg/kg bw
Method	EPA OPP 83-3
Year	1988
GLP	Yes
Test substance	Other TS: p-cresol. purity = 98.93%
Remark	p-Cresol was administered in corn oil.
Result	Maternal toxicity including audible respiration, ocular discharge, hypoactivity and death were seen at 50 mg/kg bw/day or above. pCresol had no effects on the developing

embryos at any of the doses tested.

Reliability : (1) valid without restriction

(15)

Species : Rat
Sex : Male/female
Strain : Sprague-Dawley
Route of admin. : Gavage
Exposure period : 10 weeks prior to mating through life
Frequency of treatm. : Daily
Duration of test : Lifelong
Doses : 0, 30, 175, 450 mg/kg bw/day; 25 animals/sex/group
Control group : yes, concurrent vehicle
NOAEL maternal tox. : = 175 mg/kg bw
NOAEL teratogen. : = 175 mg/kg bw
Method : Other: EPA OPP 834
Year : 1989
GLP : Yes
Test substance : Other TS: p-cresol, purity >98%

Remark : Developmental endpoints were also monitored in the 2-generation reproduction studies in rats discussed previously. Groups of rats were administered p-cresol in corn oil. Exposure began 10 weeks prior to breeding and continued in the females throughout mating, gestation and lactation.. The offspring were gavaged with the same doses as their respective parents for 11 weeks; the females again being dosed throughout mating, gestation and lactation. The F2 offspring were sacrificed at weaning.

Result : p-Cresols caused effects on pup bodyweight at some time during development when given at 450 mg/kg bw/day; a dose causing overt parental toxicity. Occasional bodyweight changes were seen at lower doses but it is not clear if these were treatment-related.

Reliability : (1) valid without restriction

(14)

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APPENDIX J
ROBUST SUMMARIES FOR o-CRESOL TOXICITY STUDIES SUPPORTING THE MIXED XYLENOLS CATEGORY

REPEATED-DOSE TOXICITY

Type	:	Repeat dose
Species	:	Rat
Sex	:	Male/female
Strain		Fischer 344
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.		ad libitum
Post exposure period		None
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group		yes, concurrent no treatment
NOAEL		83 - 87 mg/kg bw
LOAEL		242 - 256 mg/kg bw
Method		EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance		other TS: purity > 98%
Remark	:	Groups of five rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result		There were no deaths. Decreased mean final body weights in high-dose females; body weight gains and feed consumption occurred in both the top-dose males and females. Increased liver and kidney weights were recorded in the top two dose groups. Relative liver and kidney weights were increased in the top three and top two dose groups for males and females, respectively. No gross or histopathologic lesions were noted at necropsy.
Reliability	:	(1) valid without restriction

(1)

Type	Repeat dose
Species	Mouse

Sex	: male/female
Strain	: B6C3F1
Route of admin.	: oral feed
Exposure period	: 28 days
Frequency of treatm.	: ad libitum
Post exposure period	: None
Doses	: 0, 300, 1000, 3000, 10000, 30000 ppm
Control group	: yes, concurrent no treatment
NOAEL	: 50 - 60 mg/kg bw
LOAEL	: 60 - 163 mg/kg bw
Method	: EPA OTS 795.2600
Year	: 1992
GLP	: Yes
Test substance	: other TS: purity > 98%

Remark : Groups of five mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination.

At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.

Result : Mean final body weights and mean body weight gains reduced for males at top two dose groups; feed consumption was depressed at the beginning of the study in males top two dose levels. Clinical signs of toxicity, including hunched posture, rough hair coat and lethargy, were noted in high-dose animals. Hypothermia, rapid breathing and tremors were noted in the top-dose males. Relative liver weight was increased in the three highest dose groups. Relative kidney weights were increased in high-dose females. No gross lesions were noted at necropsy. Histopathological evaluation revealed ovarian atrophy in the high dose and uterine atrophy in the top dose levels.

Reliability : (1) valid without restriction

(1)

Type	: Repeat dose
Species	: Rat
Sex	: male/female
Strain	: Sprague-Dawley
Route of admin.	: Gavage
Exposure period	: 13 weeks
Frequency of treatm.	: 7 days/week
Doses	: 0, 50, 175,600 mg/kg bw/day
Control group	: Yes
LOAEL	: 50 mg/kg bw
Method	: other

Year
GLP : no data
Test substance : no data

Remark : Groups of 30 rats/sex were administered p-cresol in corn oil. The original data are unpublished and are available from the US EPA Freedom of Information Office. No further experimental details are available from the citing reviews (ATSDR, 1990; IPCS, 1993).

Result : 600 mg/kg: Mortality in 19/30 females and 9/30 males. Overt signs of toxicity at this dose included CNS depresion, lethargy, tremors, and convulsions occurring within one hour post-dosing but not beyond one hour post-dosing. High-dose male body weight gain suppression. No effects on clinical chemistry, hematology, urinalysis, no treatment-related ophthalmic lesions, no effect on organ weights, no treatment-related gross or microscopic lesions.

Reliability : (2) valid with restrictions

(2)

Type : Repeat dose
Species : Rat
Sex : male/female
Strain : Fischer 344
Route of admin. : oral feed
Exposure period : 90 days
Frequency of treatm. : Ad libitum
Post exposure period : None
Doses : 0, 1880, 3750, 7500, 15000 9r 30000 ppm
Control group : yes, concurrent no treatment
LOAEL : 7500 ppm (relative and absolute liverweight)
NOAEL : 15000 ppm

Year : 1992
GLP : **No**
Test substance : other TS: purity > 98%

Remark : Groups of 20 rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination.

At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.

Result : There were no deaths. Decreased mean final body weights in high-dose males; body weight gains and feed consumption occurred in both males

and females of the top two doses. Increased liver and kidney weights were recorded in the top two dose groups (three dose groups for liver weight). Relative testes weight was increased in high-dose males and relative thymus weight was increased in males of the top two dose groups. There was evidence of increased bone marrow hypocellularity in males of the top dose and females of the top two doses.

Reliability : (1) valid without restriction

(1)

Type : Repeat dose
Species : Mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 90 days
Frequency of treatm. : Ad libitum
Post exposure period : None
Doses : 0, 1250, 2500, 5000, 10000 or 20000 ppm
Control group : yes, concurrent no treatment
NOAEL : 2500 ppm (female body weight)
LOAEL : 5000 ppm

Year : 1992
GLP : No
Test substance : other TS: purity > 98%

Remark : Groups of 10 mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination.

At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.

Result : Mean final body weights and mean body weight gains reduced for males at the top dose and females of the top three dose groups; feed consumption was depressed at the beginning of the study in the high-dose groups. Clinical signs of toxicity included hunched posture, rough hair coat were noted in high-dose male animals. All male dose groups and females of the three highest dose groups had relative liver weight increases. Relative kidney weights were increased in high-dose females. High-dose males had increased relative testes weight. Relative thymus weight was increased in high-dose animals. Histopathological evaluation revealed minimal forestomach atrophy in the high dose groups.

Reliability (1) valid without restriction

(1)

GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, 100, 1535, 1537.
Test concentration	:	0.0, 3.3, 10.0, 33.0, 100.0, 333.0 ug/plate in water as solvent
Metabolic activation		with and without
Result	:	Negative
Method	:	other: preincubation methodology according to Ames, Mutat. Res. 31, 347 (1975) and Yahagi, Cancer Lett. 1, 91 (1975); to select dose range the chemical was checked for toxicity to S. typh. TA1 00
Year	:	1983
GLP	:	no data
Test substance	:	other TS: purity >97%
Remark		This endpoint had been studied by other investigators and results are similar to the study mentioned above.
Reliability	:	(1) valid without restriction

(3)

Type	:	Cytogenetic assay
System of testing	:	Chinese hamster ovary cells
Test concentration	:	30 to 902 ug/ml
Cycotoxic concentr.		
Metabolic activation	:	with and without
Result	:	Positive
Method	:	other: similar to OECD Guideline 473
GLP	:	Yes
Test substance	:	other TS: 99.8% pure
Method		Duplicate CHO cultures were incubated with 15-301 ug/ml of the test substance in the nonactivation aberrations assay. The metabolic activation cultures were treated with 30-300 ug/ml of the test substance in a 10 hour assay and with 301-902 ug/ml in a 20 hour assay.
Result	:	Increases in chromosomally aberrant cells were observed in the nonactivation assay at all doses. Increases in the chromosomally aberrant cells were observed in the 20 hour assay with metabolic activation at 301 and 601 ug/ml.
Reliability	:	(1) valid without restriction

(4)

Type	:	other: cell transformation assay
System of testing	:	mouse BALB/c-3T3 cells
Test concentration		0.81 nl/ml, 3.25 nl/ml, 5 and 15 nl/ml
Cycotoxic concentr.	:	31.3 nl/ml
Metabolic activation		Without
Result	:	Positive
Method	:	EPA OTS 795.2850

Year : 1988
GLP : Yes
Test substance : other TS: 99.8% pure

Reliability : (1) valid without restriction

(5)

Type : Mouse lymphoma assay
System of testing : L5178Y mouse lymphoma cells

Metabolic activation : with and without
Result : Negative
Method : other: similar to OECD Guide-line 476
Year : 1988
GLP : Yes
Test substance : other TS: 99.8% pure

Reliability : (1) valid without restriction

(6)

Type : DNA damage and repair assay
System of testing : E. coli

Metabolic activation : With and without
Result : Negative
Method : Other
Year : 1980
GLP : no data
Test substance : other TS: o-cresol, purity not noted
Flag : Critical study for SIDS endpoint

(7)

Type : Sister chromatid exchange assay
System of testing : human lymphocytes
Test concentration : O-O.5 Mm

Metabolic activation : no data
Result : Negative, Equivocal
Method : Other
Year : 1986
GLP : no data
Test substance : other TS: o-cresol, 99.9% purity

Remark : Styrene-7,8-oxide acted as the positive control. Cells were incubated with p-cresol for 88-90 hr before being analysed.
This endpoint had been studied by another investigator and reported results similar to the study mentioned above.

(8) (9)

Type : Unscheduled DNA Synthesis

System of testing : Rat hepatocytesi

Result : Negative
Method : Other
Year : 1981
GLP : no data
Test substance : other TS: o-cresol, purity not noted

(10)

Type : *In* **Vitro** Cell Transformation
System of testing : BALB 3T3

Result : **Negative**

Year : **1981**
GLP : **No data**
Test substance : **o-cresol**

(11)

GENETIC TOXICITY 'IN VIVO

Type : Dominant lethal assay
Species : Mouse
Sex : male/female
Strain : ICR
Route of admin. : Gavage
Exposure period : Single dose
Doses : 0, 75, 250, and 750 mg/kg
Result : Negative
Method : EPA OTS 798.5450
Year : 1989
GLP : Yes
Test substance : other TS: 99.8% pure

Reliability : (1) valid without restriction

(12)

Type : Drosophila SLRL test
Species : Drosophila melanogaster
Sex : Male
Strain : other: Oregon-R
Route of admin. : oral feed
Exposure period : 3 days
Doses : 0, 100,500 and 1000 ug/ml 5% sucrose
Result : Negative
Method : EPA OTS 798.5275
Year : 1989

GLP	**: Yes**
Test substance	: Other TS: 99.8% purity
Reliability	: (1) valid without restriction

(13)

TOXICITY TO FERTILITY

Type	: Two generation study
Species	: Rat
Sex	: male/female
Strain	: Sprague-Dawley
Route of admin.	: Gavage
Exposure period	: see remarks
Frequency of treatm.	: 5 days per week
Premating exposure period	
Male	: 10 weeks
Female	: 10 weeks
Duration of test	: see remarks
No. of generation studies	:
Doses	: 0, 30, 175,450 25 rats/sex/group
Control group	: yes, concurrent vehicle
NOAEL parental	: ca. 30 mg/kg bw
NOAEL F1 offspring	: ca. 175 mg/kg bw
NOAEL F2 offspring	: ca. 175 mg/kg bw
other: NOAEL (fertility)	: ca. 450 mg/kg bw
Method	: EPA OPP 83-4
Year	: 1989
GLP	**: Yes**
Test substance	: other TS: 98.93% pure

Remark : Groups of rats were administered o-cresol in corn oil. Exposure began 10 weeks prior to breeding and continued in the females throughout mating, gestation and lactation. The offspring were gavaged with the same doses as their respective parents for 11 weeks; the females again being dosed throughout mating, gestation and lactation. The F2 offspring were sacrificed at weaning.

Result : Clinical signs of toxicity occurred in FO and F1 males and females at 450 mg/kg bw/day and included hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration, perinasal encrustation (not in FO males), and perioral wetness occurred at >= 175 mg/kg bw.

No reproductive parameters were effected in either of the two generations (F1 or F2).
o-Cresol caused increased still births in the F1 and F2 generations: in F1 pups at 175 (but not 450) mg/kg/day and in F2 pups at 30 and 450 (but not 175) mg/kg/day. There was some variability in the number of stillborn in control

		groups in Fl and F2 generation (2 versus 6) and there was no clear dose-dependent effect in both generations (control/low/mid/high dose: F1 pups: 2/4/1 3/6; F2 pups: O/7/4/9). In F2 (but not F1) live birth indices were reduced at 30 and 450 (not 175) mg/kg/day. Without any other effects especially in the 30 mg/kg bw-group it is unclear whether the effects on live birth indices were substance related. Pup survival indices in both generations were not affected by treatment.
Reliability	:	(1) valid without restriction

(14)

DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	.	Rat
Sex	:	Female
Strain		Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	days 6-15
Frequency of treatm.	.	Daily
Duration of test	:	10 days
Doses		0, 30, 175, 450 mglkg bw/day; 25 inseminated females/group
Control group	.	yes, concurrent vehicle
NOAEL maternal tox.	:	= 175 mglkg bw
NOAEL teratogen.	:	= 175 mg/kg bw
Method	.	EPA OPP 83-3
Year		1988
GLP	.	Yes
Test substance	.	Other TS: o-cresol, purity = 98.93%
Remark		o-Cresol was administered in corn oil.
Result	:	Maternal toxicity occurred at 450 mglkg bw/day and included death, decreased food consumption and body weight gain, audible respiration, hypoactivity, ataxia and tremors. There was no treatment-related increased incidence of malformations at any dosage.
Reliability	.	(1) valid without restriction

(15)

Species	:	Rabbit
Sex	:	Female
Straln	:	New Zealand white
Route of admin.	:	Gavage
Exposure period		Days 6-18 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	24 days
Doses	:	0, 5, 50, 100 mg/kg bw/day; 14 inseminated females/group
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	5 mglkg bw
NOAEL developmental	.	50 mglkg bw
Method	:	EPA OPP 83-3
Year		1988

GLP	:	**Yes**
Test substance	:	Other TS: o-cresol, purity = 98.93%
Remark	:	o-Cresol was administered in corn oil.
Result	:	Maternal toxicity including audible respiration, ocular discharge were seen at 50 mg/kg bw/day or above. o-Cresol had no effects on the developing embryos at any of the doses tested.
Reliability	:	(1) valid without restriction

(16)

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APPENDIX K
ROBUST SUMMARIES FOR MIXED CRESOL ISOMERS TOXICITY STUDIES SUPPORTING THE MIXED XYLENOLS CATEGORY

REPEATED-DOSE TOXICITY

Type	: Repeat dose
Species	: Rat
Sex	: Male/female
Strain	: Fischer 344
Route of admin.	: oral feed
Exposure period	: 28 days
Frequency of treatm.	: ad libitum
Post exposure period	: None
Doses	: 0, 300, 1000, 3000, 10000, 30000 ppm
Control group	: yes, concurrent no treatment
NOAEL	: 300 ppm
LOAEL	: 1000 ppm nasal respiratory hyperplasia in females
Method	: EPA OTS 795.2600
Year	: 1992
GLP	: Yes
Test substance	: m/p-cresol, 60%-40% mix TS: purity > 98%

Remark : Groups of five rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination.

At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all contrds, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.

Result There were no deaths. Decreased mean final body weights in high-dose males; body weight gains and feed consumption occurred in both the top-dose males and females. Increased relative kidney weights were recorded in the top two dose groups of each sex. Relative liver weights were increased in the top three and top four dose groups for males and females, respectively. High-dose males had an increased relative testes weight. No gross lesions were noted at necropsy. Hyperplasia of the respiratory, epithelium of the nasal cavity was observed in the top three dose levels, both sexes. Mild-to-moderate bone marrow hypoplasia was seen in the top three male dose groups and the top two female dose groups. Minimal-to-mild esophagus and forestomach hyperplasia was reported for males and females of the top three dose groups.

Reliability : (1) valid without restriction

(1)

Type : Repeat dose
Species : Mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 28 days
Frequency of treatm. : ad libitum
Post exposure period : None
Doses : 0, 300, 1000, 3000, 10000, 30000 ppm
Control group yes, concurrent no treatment
NOAEL : 50-60 mg/kg bw
LOAEL : 60-163 mg/kg bw
Method : EPA OTS 795.2600
Year 1992
GLP : Yes
Test substance m/p-cresol, 60%-40% mix TS: purity > 98%

Remark : Groups of five mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination.

At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.

Result There were no unschedule deaths in the study. Mean final body weights and mean body weight gains were reduced for high-dose males and females. Body weight gain was suppressed in the top three dose groups of males. Feed consumption was depressed at the beginning of the study. Clinical signs of toxicity in high-dose animals were: alopecia, dehydration, hunched posture, rough hair coat, hypothgermia and lethargy. Relative liver weight was increased in the four highest dose groups of males and the three highest dose groups of females. High-dose males had a relative increase in testes weight. High-dose fermales had increased relative kidney weights. No gross lesions were noted at necropsy. Histopathological evaluation revealed epithelial hyperplasia of varying degrees throughout the respiratory tract.

Reliability (1) valid without restriction

(1)

Type : Repeat dose
Species : Rat
Sex : male/female
Strain : Fischer 344

Route of admin.	: oral feed
Exposure period	: 90 days
Frequency of treatm.	. Ad libitum
Post exposure period	: None
Doses	: 0, 1880, 3750, 7500, 15000 or 30000 ppm
Control group	: yes, concurrent no treatment
LOAEL	: 7500 ppm (relative and absolute liver weight)
NOAEL	: 15000 ppm
Year	: **1992**
GLP	: **No**
Test substance	: m/p-cresol, 60%-40% mix TS: purity > 98%
Remark	: Groups of 20 rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	: There were no deaths. Decreased mean final body weights in the two highest-dose males and female groups; feed consumption suppressed in high-dose groups of both sexes in first week of study. Increased relative kidney weights were recorded in the top three male dose groups and the top female dose group. Relative liver weight was elevated for animals of the top three dose groups. Relative testes weight was increased in the top two male dose groups. There was dose-related evidence of hyperplasia of the nasal respiratory epithelium. Thyroid follicle changes (increased colloid formation) was reported for males and females in a dose-related manner. Minimal increased bone marrow hypocellularity was reported for males of the top dose and females of the top dose group. Minimal-to-mild uterine atrophy was reported for the two top dose groups.
Reliability	: (1) valid without restriction

(1)

Type	: Repeat dose
Species	: Mouse
Sex	: male/female
Straln	: B6C3F1
Route of admin.	: oral feed
Exposure period	: 90 days
Frequency of treatm.	: Ad libitum
Post exposure period	: None
Doses	: 0, 625, 1250, 2500, 5000, 10000 ppm
Control group	: yes, concurrent no treatment
NOAEL	: 2500 ppm (female body weight)
LOAEL	: 5000 ppm

Year	:	1992
GLP	:	No
Test substance	:	m/p-cresol, 60%-40% mix TS: purity > 98%
Remark	:	Groups of 10 mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no unscheduled deaths during the study. Mean final body weights and mean body weight gain (males) were reduced for high-dose animals; feed consumption was slightly depressed in the high-dose groups. Male dose groups (top two dose groups) and females of the highest dose groups had relative liver weight increases. There were no liver lesions reported from microscopic examination. Histopathological evaluation revealed hyperplasia of the nasal respiratory epithelium.
Reliability	:	(1) valid without restriction

(1)

GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 97, TA 98, 100, 1535.
Test concentration	:	0.0, 10.0, 33.0, 100.0, 333.0, 1000 and 3333 or 6666 ug/plate
Metabolic activation	:	with and without hamster and rat S-9
Result	:	Negative
Method	:	Method of Zeiger, et al., 1988.
Year		1990
GLP	:	no data
Test substance	:	m-/p-cresol 60%/40% mixture; other TS: purity >97%
Remark	:	This endpoint had been studied by other investigators and results are similar to the study mentioned above.
Reliability	:	(1) valid without restriction

Type	:	Mouse lymphoma assay
System of testing		L5178Y mouse lymphoma cells

Metabolic activation : with and without
Result : Positive with, weakly positive without
Method : other: similar to OECD Guideline 476
Year : 1980
GLP : Yes
Test substance : 1 :1 :1 mixture of o-, m-, p-cresol iosmers

Reliability : (1) valid without restriction

(2)

Type : Sister chromatid exchange assay
System of testing : Chinese hamster ovary cells

Metabolic activation . With and without
Result : Positive with and without
Method : Other
Year : 1980
GLP : Yes
Test substance : 1:1:1 mixture of o-, m-, p-cresol iosmers

(2)

Type : . Cell transformation
System of testing : Mouse BALB/C 3T3 cells

Metabolic activation : With
Result : Positive
Method : Other
Year : 1980
GLP : Yes
Test substance : 1:1 :1 mixture of o-, m-, p-cresol iosmers

(2)

Type : Unscheduled DNA Synthesis
System of testing : Rat hepatocytes

Result : Positive
Method : Other
Year : 1980
GLP : Yes
Test substance : 1:1:1 mixture of o-, m-, p-cresol iosmers

(3)

GENETIC TOXICITY "IN VIVO"

Type : Micronuclei in peripheral blood erythrocytes
Species : Mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : Oral feed
Exposure period : Daily for 13 weeks
Doses : 0, 625, 1250, 2500, 5000, 10000 ppm
Result : Negative

Method	:	MacGregor et al, 1983; 10000 normochromic etythrocytes were scored for each animal
Year	:	**1990**
GLP	:	**Yes**
Test substance	:	m/p-cresol, 60%-40% mix TS: purity > 98%
Reliability	:	(1) valid without restriction

(1)

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APPENDIX L
ROBUST SUMMARIESY FOR XYLENOL ISOMERS TOXICITY STUDIES SUPPORTING THE MIXED XYLENOLS CATEGORY

Type : Ames test
System of testing : Salmonella typhimurium TA 98 and TA100.

Metabolic activation : with and without
Result : Negative
Method : Not stated
Year : 1979
GLP : No data
Test substance : 2,3-xylenol
Reliability : Limited

(1)

Type : Acute aquatic invertebrate
System of testing : Static bioassay
Test Organism : Daphnia magna
Duration of test : 48 hr

Result : LC50 = 16.0 mg/L

Year : 1975
GLP : No data
Test substance : 2,3-xylenol

Reliability : Limited

(2)

Type : Acute toxicity
System of testing : Oral gavage
Test species : Rat

Result : Acute oral LD50 = 2300 mg/kg
Method : Not stated
Year : 1996
GLP : no data
Test substance : 2,4-xylenol

Reliability : Limited

(3)

Type : Repeat dose
Species : Mouse
Sex : male/female
Strain : Albino
Route of admin. : oral gavage
Exposure period : 90 days
Frequency of treatm. : Once per day

Post exposure period	:	None
Doses	:	0, 5, 50 or 250 mg/kg/day
Control group	:	Yes, concurrent no treatment and corn oil (vehicle) control
NOAEL	:	50 mglkg bw
LOAEL	:	250 mg/kg bw
Method	:	Not stated
Year	:	1989
GLP	:	No
Test substance	:	2,4-xylenol
Remark	:	Groups of 30 mice/sex/dose were tested. Mortality, clinical signs, body weight, feed consumption, ophthalmology, hematology, clinical chemistry, organ weights and gross and microscopic pathology were recorded.
Result	:	No significant differences were found between treated and the vehicle control group in body weight, body weight gain, food consumption or. ocular effects. High-dose animals displayed squinting, lethargy, prostration, and ataxia. There were no gross or microscopic differences in organ weights due to treatment.
Reliability	:	(1) valid without restriction

(4)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98 and TA100.
Metabolic activation	:	with and without
Result	:	Negative
Method	:	Not stated
Year	:	1979
GLP	:	No data
Test substance	:	2,4-xylenol
Reliability	:	Limited

(1)

Type	:	Acute aquatic vertebrate
System of testing	:	Flowthrough bioassay
Test Organism	:	Fathead minnow
Duration of test	:	96 hr
Result	:	LC50 = 17.0mg/L
Year	:	1981
GLP	:	No data
Test substance	:	2,4-xylenol
Reliability	:	Limited

(5)

Type	:	Acute toxicity
System of testing	:	Oral gavage
Test species	:	Rat

Result	:	Acute oral LD50 = 444 mg/kg
Method		Not stated
Year	:	1996
GLP	:	no data
Test substance		2,5-xylenol
Reliability		Limited

(3)

Type		Ames test
System of testing	:	Salmonella typhimurium TA 98 and TA100.
Metabolic activation	:	with and without
Result	:	Negative
Method		Not stated
Year		1979
GLP		No data
Test substance	:	2,5-xylenol
Reliability	:	Limited

(1)

Type		Acute aquatic invertebrate
System of testing	:	Static bioassay
Test Organism	:	Daphnia magna
Duration of test	:	48 hr
Result		LC50 = 10.0 mg/L
Year		1975
GLP		No data
Test substance		2,5-xylenol
Reliability		Limited

(2)

Type	:	Acute aquatic vertebrate
System of testing	:	Static bioassay
Test Organism	:	Rainbow trout
Duration of test	:	96 hr
Result		LC50 = 3.2-5.6 mg/L
Year	:	1983
GLP	:	No data
Test substance		2,5-xylenol
Reliability		Limited

(6)

Type	:	Acute toxicity
System of testing		Oral gavage

Test species : Rat

Result : Acute oral LD50 = 296 mg/kg
Method : Not stated
Year : 1996
GLP : no data
Test substance : 2,6-xylenol

Reliability : Limited

(3)

Type : Repeat dose
Species : Rats
Sex : Not stated
Strain : Not stated
Route of admin. : Oral gavage
Exposure period : 8 months
Frequency of treatm. : Once per day
Post exposure period : None
Doses : 0, 0.6 or 6.0 mg/kg/day
Control group : Yes, concurrent no treatment
NOAEL : 0.6 mg/kg bw
LOAEL : 6.0 mg/kg bw
Method : Not stated
Year : 1979
GLP : No
Test substance : 2,6-xylenol

Result : No effects were reported for the low dose group. The high-dose group was reported to exhibit body weight changes, blood pressure changes, changes in protein sulfhydryl groups in blood serum and internal organs, and histopathological changes in the kidney, liver and spleen.
Reliability : Limited

(7)

Type : Ames test
System of testing : Salmonella typhimurium TA 98 and TA100.

Metabolic activation : with and without
Result : Negative
Method : Not stated
Year : 1979
GLP : No data
Test substance : 2,6-xylenol
Reliability : Limited

(1)

Type : Mammalian bone marrow cytogenetics
Species : Rats
Sex : Male and female
Strain : CD Sprague-Dawley

Route of admin.	: Oral gavage
Exposure period	: One day
Frequency of treatm.	: Once per day
Post exposure period	: 36 hours
Doses	: 0,350, 700 or 1400 mg/kg/day (males); 0, 300, 600 or 1200 mg/kg/day (females)
Control group	: Yes, concurrent no treatment
NOAEL	: 1400 mg/kg bw (males) 1200 mg/kg/day (females)
LOAEL	: Not determined
Method	: OECD 475 (1984)
Year	: 1996
GLP	: Not stated
Test substance	: 2,6-xylenol
Result	: Bone marrow cells collected at 12, 24 or 36 hours post dosing were examined microscopically for structural chromosome aberrations. No significant increases in percentage of aberrant cells were observed in any treatment group or at any marrow harvest time.
Reliability	: (1) valid without restriction

(8)

Type	: Developmental toxicity
Species	: Rats
Sex	: Female
Strain	: CD Sprague-Dawley
Route of admin.	: Oral gavage
Exposure peripd	: Gestation days 6-15
Frequency of treatm.	: Once per day
Post exposure period	: 5 days
Doses	: 0, 60, 180 and
Control group	: Yes, concurrent no treatment
NOAEL	: 60 mg/kg bw (maternal) 180 mg/kg/day (developmental)
LOAEL	: Not determined
Method	: OECD414
Year	: 1997
GLP	: Not stated
Test substance	: 2,6-xylenol
Result	: 24 rats per group. Maternal body weight (during gestation) and weight gain were depressed in the mid-dose group. Maternal mortality occurred (2124) in the high-dose group; body weight loss, weight gain suppression and decreased food consumption occurred. Pups from high-dose females had a reduction in fetal body weight.
Reliability	: (1) valid without restriction

(9)

Type	: Acute aquatic vertebrate
System of testing	: Flow through bioassay
Test Organism	: Rainbow trout
Duration of test	: 96 hr

Result : LC50 = 27 mg/L

Year : 1983
GLP : No data
Test substance : 2,6-xylenol

Reliability : Limited

(5)

Type : Acute aquatic invertebrate
System of testing : Static bioassay
Test Organism : Daphnia magna
Duration of test : 48 hr

Result : LC50 = 11.2 mg/L

Year : 1974
GLP : No data
Test substance : 2,6-xylenol

Reliability : Limited

(10)

Type : Acute aquatic plant
System of testing : Static bioassay
Test Organism : Tetrahymena pyriformis
Duration of test : 24 hr

Result : LC100 = 325 mg/L

Year : 1978
GLP : No data
Test substance : 2,6-xylenol
Remark : Another investgator reports a duckweed LC50 of 460,000 mg/L for 2,6-xylenol (Blackman, G. E. et al, Arch, Biochem. Biophysics., 54, 45-54, 1955)

Reliability : Limited

(11)

Type : Acute toxicity
System of testing : Oral gavage
Test species : Mouse

Result : Acute oral LD50 = 400 mg/kg
Method : Not stated
Year : 1996
GLP : no data
Test substance : 3,4-xylenol

Reliability : Limited

(3)

Type : Ames test
System of testing : Salmonella typhimurium TA 98 and TA100.

Metabolic activation : with and without
Result : Negative
Method : Not stated
Year : 1979
GLP : No data
Test substance : 3,4-xylenol
Reliability : Limited

(1)

Type : Acute aquatic vertebrate
System of testing : Static
Test Organism : Fathead minnow
Duration of test : 48 hr

Result : LC50 = 15 mg/L

Year : 1983
GLP : No data
Test substance : 3,4-xylenol

Reliability : Limited

(6)

Type : Acute toxicity
System of testing : Oral gavage
Test species : Rat

Result : Acute oral LD50 = 608 mg/kg
Method : Not stated
Year : 1996
GLP : no data
Test substance : 3,5-xylenol

Reliability : Limited

(3)

Type : Acute aquatic vertebrate
System of testing : Not stated
Test Organism : Crucian carp

Duration of test : 24 hr

Result : TLm = 53 mg/L

Year : **1983**
GLP : No data
Test substance : 3,5-xylenol

Reliability : Limited

(6)

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